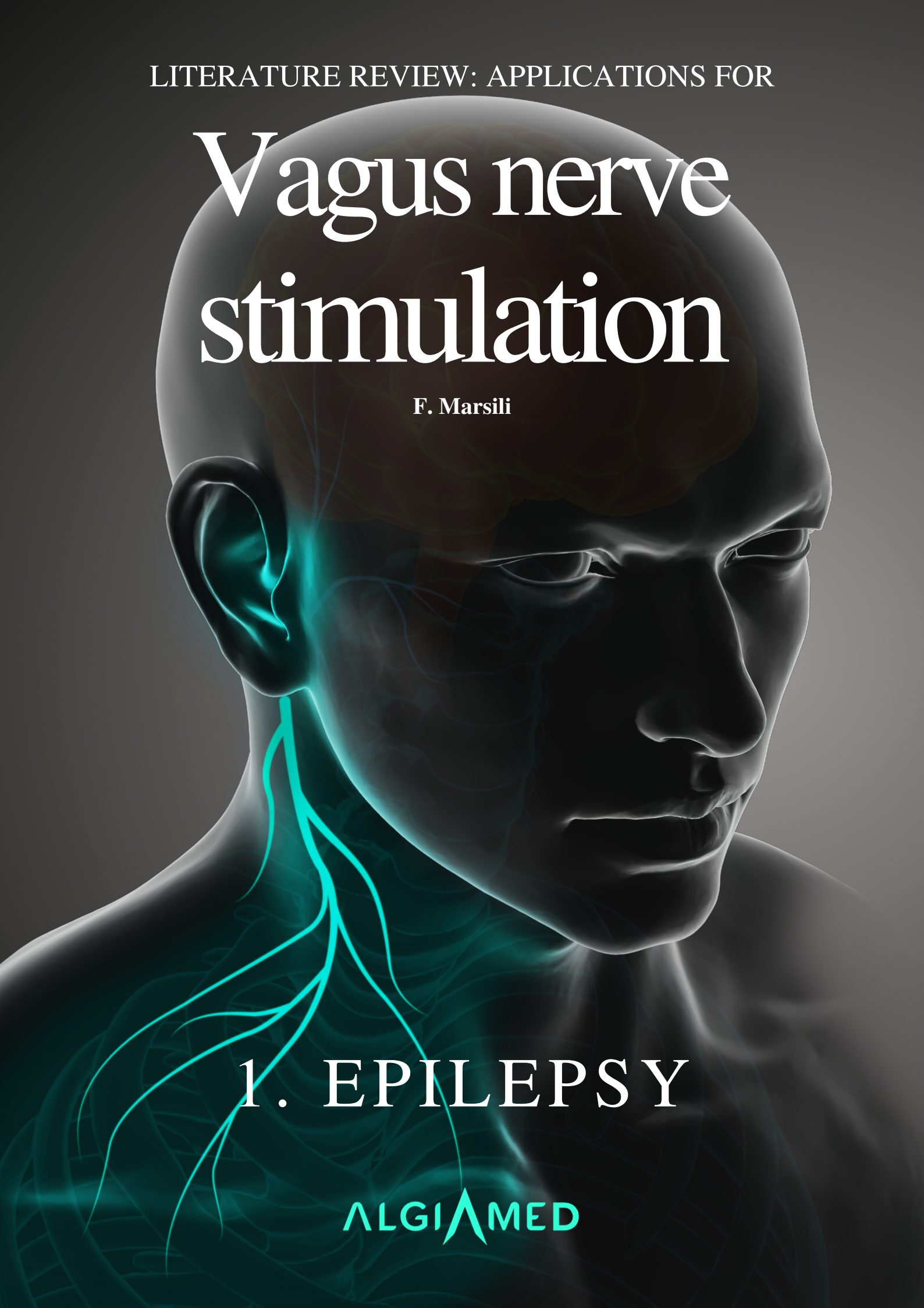
LITERATURE REVIEW: APPLICATIONS FOR

Vagus nerve stimulation

F. Marsili



1. EPILEPSY

ALGIAMED

Author's choice

The papers in this collection focus on the application of Vagus Nerve Stimulation (VNS) as established therapeutic solution for difficult-to-treat conditions.

The vagus nerve is the longest cranial nerve and is widely distributed throughout the body, traversing the neck, thorax and abdomen. It is composed by motor fibres and sensory fibres from sympathetic and parasympathetic branches. [1], [2]. Afferent branches of the vagus nerve innervate brain behavioural areas involved in depressive states, and it desynchronises cortical activity with anti epileptic effects [3], [4]. Efferent branches of the vagus nerve regulate gastrointestinal secretory and motor function [5]. Recent advances in the field, have unraveled an anti-inflammatory role of the efferent vagus nerve via the Cholinergic Anti-inflammatory Pathway (CAP), a known mechanism for neural inhibition of inflammation linked to the activation of the autonomic nervous system (ANS) [6], [7].

Electrical stimulation of the VN modulates the nervous system at central, peripheral, and autonomic levels without the need for pharmacological interventions. For decades, invasive techniques of VNS have demonstrated their clinical efficacy in VN-related diseases and, to these days, efforts have been made to create a more safe, effective, and non-invasive solution to VNS.

The auricular branch is the only peripheral branch of the VN on the human body, it is part of the afferent portion of the VN that directly connects to the brainstem. Thus, auricular VN has become the most favourable access point for non-invasive VNS. Neuroimaging studies on animal models and humans have confirmed the modulatory efficacy of auricular VNS (aVNS). For examples, fMRI studies show identical activation patterns in the brain between invasive and aVNS, with significant inhibitory and anti-inflammatory effects. Due to the existence of different control systems, the anti-inflammatory effects of aVNS (i.e., release of norepinephrine and noradrenaline, and neurotrophic factors) seem to occur immediately after intervention, while neuroplastic changes only occur as a consequence of sustained regenerative efforts [7].

Colleciton 1 and collection 2 are the most extensive selections, since VNS has been standard-of-care for epilepsy and depression for decades. Collection 3 explores the possibility of using VNS for the treatment of posttraumatic stress disorders. Collection 4 focuses on fibromyalgia and collection 5 on multiple sclerosis. Collection 6 and 7 corroborates the hypothesis that VNS can be used to activate the cholinergic anti-inflammatory pathway to treat inflammatory diseases, such as inflammatory bowel disease or rheumatoid arthritis. Collection 8 and 9 focus on the use of VNS for ameliorating pain sensitivity in chronic pain conditions and for rehabilitating upper limb motor fibres after ischemic strokes, respectively. In conclusion, collection 10 opens up other possibilities for clinical applications of VNS, ranging from cardiovascular diseases, through ADHD disorders, to tinnitus.

To summarise, VNS is a novel technology and its non-invasive configuration is still under investigation. Further clinical examinations are mandatory in order to understand the underlying mechanism of VNS and to open the door to new possible therapeutic applications. However, being a non-invasive, safe, and efficient therapeutic solution, VNS is an attractive tool for further implementation and new creative clinical applications.

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1. VNS and epilepsy

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FULL-LENGTH ORIGINAL RESEARCH

The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: The PuLsE (Open Prospective Randomized Long-term Effectiveness) trial

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Summary

Objective: To evaluate whether vagus nerve stimulation (VNS) as adjunct to best medical practice (VNS + BMP) is superior to BMP alone in improving long-term health-related quality of life (HRQoL).

Methods: PuLsE (Open Prospective Randomized Long-term Effectiveness) was a prospective, randomized, parallel-group, open-label, and long-term effectiveness study (conducted at 28 sites in Europe and Canada). Adults with pharmacoresistant focal seizures (n = 112) received VNS + BMP or BMP (1:1 ratio). Medications and VNS parameters could be adjusted as clinically indicated for optimal seizure control while minimizing adverse effects. Primary endpoint was mean change from baseline HRQoL (using Quality of Life in Epilepsy Inventory-89 total score; QOLIE-89). Secondary endpoints included changes in seizure frequency, responder rate (≥50% decrease in seizure frequency), Centre for Epidemiologic Studies Depression scale (CES-D), Neurological Disorders Depression Inventory-Epilepsy scale (NDDI-E), Clinical Global Impression-Improvement scale (CGI-I), Adverse Event Profile (AEP), and antiepileptic drug (AED) load. The study was prematurely terminated due to recruitment difficulties prior to completing the planned enrollment of n = 362. Results for n = 96 who had baseline and at least one follow-up QOLIE-89 assessment (from months 3-12) were included in this analysis. Mixed model repeated measures (MMRM) analysis of variance was performed on change from baseline for the primary and secondary endpoints.

Results: Significant between-group differences in favor of VNS + BMP were observed regarding improvement in HRQoL, seizure frequency, and CGI-I score (respective p-values < 0.05, 0.03, and 0.01). More patients in the VNS + BMP group (43%)

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reported adverse events (AEs) versus BMP group (21%) (p = 0.01), a difference reflecting primarily mostly transient AEs related to VNS implantation or stimulation. No significant difference between treatment groups was observed for changes in CES-D, NDDI-E, AEP, and AED load.

Significance: VNS therapy as a treatment adjunct to BMP in patients with pharmacoresistant focal seizures was associated with a significant improvement in HRQoL compared with BMP alone.

KEY WORDS: Epilepsy, Health-related quality of life, QOLIE-89, Seizures, Vagus nerve stimulation.

Vagus nerve stimulation (VNS) was approved in 1997 for use as an adjunctive therapy in patients with pharmacoresistant epilepsy.[1–3] Since then, VNS therapy has been provided to >70,000 patients worldwide, and its beneficial effects in reducing seizure frequency have been reported in multiple long-term open-label studies.[4] Other potentially relevant benefits that have been reported include decreased severity and duration of ictal or postictal phases, and improved mood, vigilance, communication, cognition, and possibility of reducing antiepileptic drugs (AEDs) and associated adverse effects.[5–10] Such benefits could have a significant impact on health-related quality of life (HRQoL), in addition to reduction in seizure frequency, and may partially explain the observation that >70% of patients choose to continue receiving VNS therapy once their battery needs to be replaced, an average of 6 years after implantation (data on file; Cyberonics, Inc., 2009; Houston, TX, U.S.A.). However, apart from seizure frequency, none of the above VNS outcomes were assessed in patients with epilepsy in the setting of a randomized controlled trial.

The PuLsE (Open Prospective Randomized Long-term Effectiveness study was designed to assess whether VNS as a treatment adjunct to best medical practice (VNS + BMP) is superior to BMP alone in improving HRQoL in patients with pharmacoresistant focal seizures.

Methods

PuLsE was an international, multicenter, prospective, randomized, parallel-group, open-label, and long-term (2 years) effectiveness study (Fig. 1; ClinicalTrials.gov identifier: NCT00522418). The primary objective was to demonstrate superiority over time in health outcomes of BMP with adjunctive VNS therapy compared with BMP alone in patients with pharmacoresistant focal seizures. A total of 28 sites across Europe and Canada participated in the study.

The design was dictated primarily by the need to ensure a relatively long duration of follow-up, in order to obtain a clinically meaningful assessment of long-term changes in HRQoL. This precluded on ethical grounds the use of a double-blind design, and required that the treating physicians be allowed to modify the regimen of AEDs as clinically indicated. Accordingly, BMP was defined as the individualized therapy judged optimal by investigators at each visit for each patient, which could include a change in dosage or type of AEDs (including their withdrawal). In a similar way, clinicians were allowed to adjust VNS stimulation parameters throughout the study. This approach has the advantage of reflecting routine clinical practice, thereby increasing the external validity of the study.

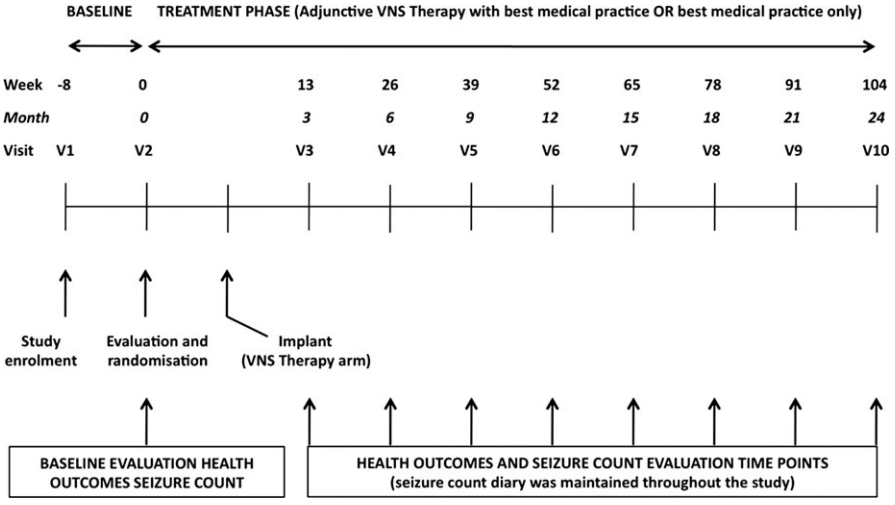

Figure 1.
Study time line showing the timing of the various study visits and efficacy assessments.
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Study participants

Eligible participants were 16–75 years old with at least a 2-year history of focal seizures not adequately controlled by ongoing AED therapy. Additional eligibility criteria were (1) previous failure of at least three AEDs used alone or in combination; (2) treatment with at least one AED with a regimen that was stable for at least 1 month prior to study entry; and (3) at least one focal seizure with a motor component per month during the 2 months prior to study entry. Patients with psychogenic nonepileptic seizures or genetic (idiopathic) generalized epilepsies were not eligible for the study. Prior to randomization, all participants provided written informed consent approved by the ethics committees at each study site.

Endpoints

The primary endpoint was the mean change from baseline in the 89-item Quality of Life in Epilepsy Inventory (QOLIE-89) total score.[11] Secondary endpoints included QOLIE-89 composite subscores (Epilepsy-targeted, Cognition, Mental Health, and Physical Health), 50% responder rate (proportion of patients with ≥50% decrease in seizure frequency vs. baseline), scores on the Centre for Epidemiologic Studies Depression scale (CES-D),[12] Neurological Disorders Depression Inventory in Epilepsy scale (NDDI-E),[13] Clinical Global Impression of Improvement scale (CGI-I),[14] and Adverse Event Profile (AEP),[15,16] and change from baseline in AED load (defined as the sum of the Prescribed Daily Dose (PDD)/Defined Daily Dose (DDD) ratios for each AED included in the treatment regimen of each individual patient).[17] Safety and tolerability were evaluated based on spontaneously reported adverse events (AEs) and premature withdrawals.

Study conduct

After a prestudy screening (visit 1), patients fulfilling the eligibility criteria entered an 8-week prospective baseline, which was used to determine baseline seizure frequency and other health outcomes, all of which were recorded at visit 2 at completion of the 8-week period (Fig. 1). During visit 2, patients who continued to meet the eligibility criteria were randomized to VNS + BMP or BMP alone (1:1 ratio) through a centralized voice-based randomization service. All treatments were prescribed and delivered according to the procedures routinely used in clinical practice in each center. In particular, centers were responsible for covering the costs involved in the acquisition of the VNS therapy device. Study visits were scheduled at 3-month intervals over a 24-month assessment period. The database for the PuLsE study was originally held by the Bonn epilepsy center (Germany). Upon closure of the study, the database was transferred to Cyberonics, where data analysis was conducted by one of the coauthor (P. Raman, employee of Cyberonics).

Statistical analyses

The initial plan was to enroll 362 patients and to follow each patient for 2 years. The original statistical analysis plan included the intent-to-treat and per-protocol populations, but such analysis was not possible because of early study termination due to low enrollment rates, requiring revision of the statistical plan. Only patients with a baseline QOLIE-89 score and at least one postbaseline assessment were included in the statistical analysis of data from 3, 6, 9, and 12 months of follow-up.

For longitudinal data collected at different visits postbaseline, we performed a mixed model repeated measures (MMRM) analysis of variance (ANOVA) using the SAS GLIMMIX (generalized linear mixed model) procedure to assess trend differences between the two treatment groups. The fitted model included fixed effects of treatment group (VNS + BMP vs. BMP), visit month (3, 6, 9 and 12 months following randomization), and interaction of treatment and visit month. The evaluated response endpoints included the primary endpoint of mean change from baseline in QOLIE-89 total scores, and changes in the following secondary endpoints: seizure frequency, 50% responder rate, CES-D, NDDI-E, CGI-I, AEP, proportion of patients reporting AEs, and AED load. An additional change in QOLIE-89 total scores was assessed in patients who had no changes in their baseline AEDs. The secondary endpoints are partially redundant with the primary endpoint; therefore, p-values from secondary endpoint analyses are being reported here for exploratory analysis purposes and correction of multiple comparisons were not conducted. When inferential statistics were conducted based on MMRM analyses, the least squares means and related standard errors were summarized. Inferential statistical analyses were not conducted for the visit-wise data, as there were limited numbers of observations, instead the visit-wise data are summarized using descriptive statistics including means, percentages, medians, standard deviation, and p-values.

When MMRM analysis results indicated significant treatment-group trend differences ($p < 0.05$), post hoc visit-wise analyses were performed using patient data at each visit. p-Values based on means were generated using analysis of variance (F-test) for continuous data. p-Values based on medians were generated using the Wilcoxon rank-sum test for continuous data. p-Values were generated using the chi-square test for categorical data.

Results

This study was conducted between February 2006 and July 2008 and was prematurely terminated by the sponsor due to a low enrollment rate and not as a result of a safety or efficacy signal. Low enrollment resulted primarily from the strong positive or negative views about the value of VNS therapy expressed by most study candidates, leading to only a minority of them accepting to participate in the study. As a

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result of early study termination, only a few patients (n = 7) achieved 2-year follow-up. The VNS therapy devices were not removed from the participating patients following study termination, and the patients continued to use their devices as part of routine medical care, as clinically indicated.

A total of 131 patients were screened and 122 were randomized to receive VNS + BMP or BMP alone. Data from one study site (including 10 randomized patients) were removed from the analysis datasets, as inadvertently a centrally approved informed consent form was used without the additional mandatory approval of the site's local ethics committee. The remaining 112 randomized patients were included in the safety analyses. Of these, 96 (83%)—including 48 patients allocated to VNS + BMP and 48 patients allocated to BMP—had baseline data and at least one post baseline follow-up QOLIE-89 assessment, and were thus included in the efficacy analyses. Sixty of these 96 patients had completed their 1-year follow-up visit by the time the study was terminated, including 55 patients with QOLIE-89 data available at each visit (assessments at 0, 3, 6, 9, and 12 months; 28 in the VNS + BMP group and 27 in the BMP group).

Of the eligible randomized patients, 16 were not included in the statistical analysis, as their study participation ended prior to collection of baseline data and at least one post-baseline follow-up QOLIE-89 assessment for the following reasons: 9 patients due to premature study termination (two from VNS + BMP group and seven from BMP group), 2 patients due to consent withdrawal (one from each treatment group), 2 patients due to compliance issues (one from each treatment group), 2 patients who withdrew early for reasons not listed (both from the VNS + BMP group), and one patient in the BMP group who withdrew early due to lack of efficacy.

Patients in the two treatment groups were comparable at baseline in terms of gender, age, age at onset of epilepsy, proportion with structural or metabolic versus unknown etiology, seizure frequency, AED load, and mean baseline scores from QOLIE-89, AEP, CES-D, NDDI-E, and CGI-I assessments (Table 1). There were no significant differences between the two treatment groups for any of the recorded baseline characteristics ($p \geq 0.05$).

Among patients in the VNS + BMP arm, there was a median interim period of 48 days (range 8–162) between randomization and implantation surgery. The duration of the preoperative waiting period varied in relation to regional and national regulations for approving reimbursement of VNS therapy in individual subjects, and the local waiting time for nonurgent neurosurgical procedures. Treatment assessments for the VNS + BMP arm were started at the initiation of VNS treatment, and each patient began VNS dose titration according to protocol-specified guidelines.

At the 12-month follow-up visit, the median VNS parameters were 1.8 mA output current (range 0.8–2.8 mA), 500 μs pulse width, 30 s signal ON time, 5 min signal OFF time, and 147.8 mC of total charge delivered per day (range 40.3–420.0 mC/day) (see Table S1 for detailed values at each follow-up visit).

HRQoL evaluation

MMRM analysis of change from baseline in QOLIE-89 score over time showed a significant difference between the two groups (48 VNS + BMP patients and 48 control patients), with a greater improvement in patients allocated to the VNS + BMP group ($p < 0.05$) (Table S2). Visit-wise ANOVA showed that the benefit of VNS + BMP was maximal at 12 months ($p = 0.01$), with a mean (± standard deviation [SD]) improvement of 5.5 (±7.2) in patients allocated to VNS + BMP (n = 31) compared with 1.2 (±6.9) in those allocated to BMP alone (n = 29) (Fig. 2). The visit-wise ANOVA data for the other time points were as follows: 3 months ($p = 0.12$; 47 VNS + BMP patients and 47 BMP patients), 6 months ($p = 0.07$; 38 VNS + BMP patients and 45 BMP patients), and 9 months ($p = 0.50$; 33 VNS + BMP patients and 35 BMP patients).

Similar improvements in QOLIE-89 score were observed for patients in the VNS + BMP subgroups who had no change in their number or type of AEDs (n = 42; $p = 0.03$), or in their AED drug load albeit not significant (n = 32; $p = 0.08$), compared with the entire BMP group (n = 48) (Table S2).

MRMM analysis of each QOLIE-89 subscales showed more improvement in patients allocated to VNS + BMP than in those receiving BMP alone; however, the differences were not significant: Epilepsy-targeted score ($p = 0.06$), Cognitive ($p = 0.20$), Mental Health ($p = 0.33$), and Physical Health ($p = 0.17$) (Table S2; visit-wise ANOVA data are provided in Table S3).

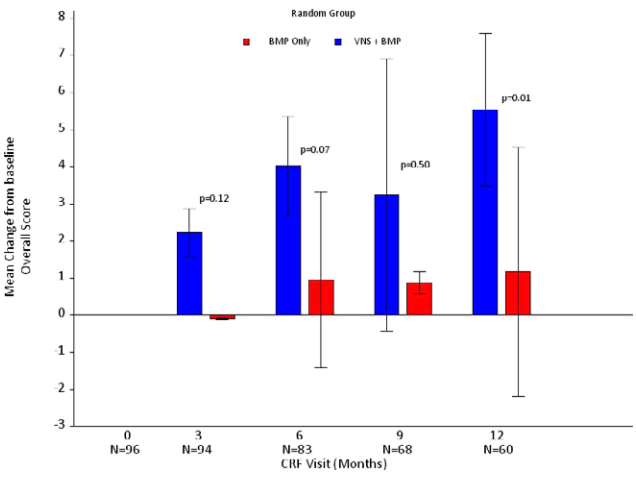

Figure 2.
Primary outcome measure: Mean change in QOLIE-89 overall score from baseline (Month 0; n = 96) to Months 3 (n = 94), 6 (n = 83), 9 (n = 68), and 12 (n = 60).
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Seizure control and CGI-I, CES-D, and NDDI-E outcomes

MMRM analysis of the change from baseline in total number of seizures per week was significantly greater in the VNS + BMP group than in the BMP group (p = 0.03). Median percent change in seizure frequency from baseline to 12 months confirms an increasing improvement in seizure control for the VNS + BMP group versus the BMP group over time, although differences at individual time points failed to reach statistical significance (Fig. 3).

MMRM analysis of the 50% responder rates did not differ significantly between the VNS + BMP group (n = 10/31; 32%) and control group (n = 7/29; 24%) at month 12 (p = 0.49) (data not shown).

MMRM analysis of changes over time in CGI-I score demonstrated a significant difference between the two groups, with greater improvement in patients allocated to the VNS + BMP group (p = 0.01) (Table 2). Visit-wise ANOVA showed that the benefit of VNS + BMP was significant for patients allocated to VNS + BMP, compared with those allocated to BMP alone at 3 and 12 months (p-values of 0.01 and 0.03, respectively), and a trend was observed at 9 months (p = 0.05) but not at 6 months (p = 0.49) (Fig. 4).

MMRM analysis of changes in CES-D and NDDI-E scores did not show significant differences between groups (p-values were 0.90 and 0.13, respectively) (Table 2). Change from baseline values at follow-up time points are provided in Table S4.

A summary of changes in underlying AED treatment is provided in Table S5. Both treatment groups had similar AED loads from baseline to follow-up time points. When change from baseline AED load was evaluated by MMRM analysis, a nonsignificant trend was observed between the groups (p = 0.08) with a greater increase in the BMP group (means ± standard error (SE): 0.18 ± 0.05) than in the VNS + BMP group (means ± SE: 0.06 ± 0.05) (data not shown).

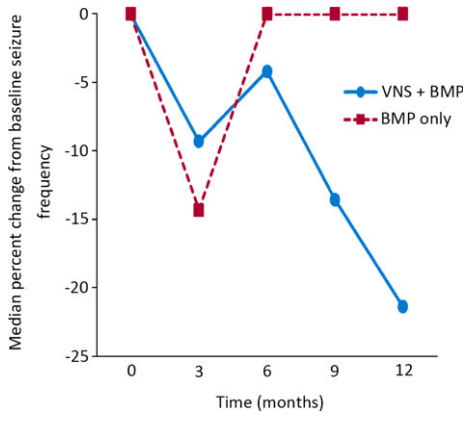

Figure 3.
Median percent change in total seizure frequency from baseline (Month 0; n = 95) to Months 3 (n = 93), 6 (n = 80), 9 (n = 67), and 12 (n = 60). p-Values at baseline, and 3, 6, 9, and 12 months were 0.94, 0.77, 0.35, 0.12, and 0.13, respectively.
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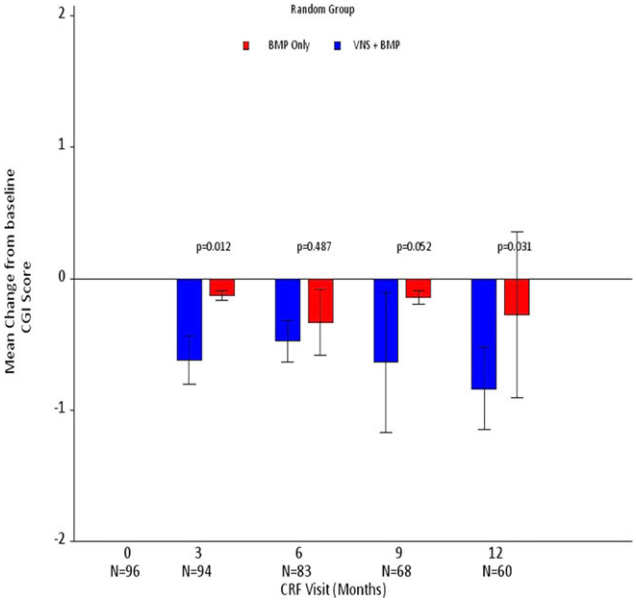

Figure 4.
Mean change in CGI-I score from baseline (Month 0; n = 96) to Months 3 (n = 94), 6 (n = 83), 9 (n = 68), and 12 (n = 60).
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AEP scores and AEs

Changes from baseline AEP values at 3, 6, 9, and 12 months are provided in Table S4. MMRM analysis of least-squares mean score (SE) was −3.7 (±1.0) in the VNS + BMP group and −1.3 (±1.0) in the BMP group, but the difference was not significant (p = 0.08) (Table 2).

At least one AE was reported in 23 patients (43%) in the VNS + BMP group and in 12 patients (21%) in the control group (p = 0.01). The majority of AEs reported in the VNS + BMP group were related to VNS therapy, that is, device implantation (n = 12; 22%) and electrode stimulation (n = 11; 20%). Specific AEs reported at a frequency of >5% were reported only in the VNS + BMP group and included dysphonia (n = 8; 15%) and chest pain, headache, hypoesthesia, and depression, each reported in 3 patients (6%). Of these AEs, chest pain (n = 3) and hypoesthesia (n = 3) were considered related to VNS device implantation; and dysphonia (n = 7) was considered related to device stimulation. In addition, one patient experienced localized infection related to device implantation.

Serious AEs were reported in five (9%) patients in the VNS + BMP group and in three (5%) patients in the BMP group. In the VNS + BMP group, these included transient vocal cord paralysis in two patients (considered to be related to the implantation procedure; both completely resolved); brief respiratory arrest of moderate severity in

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one patient from postoperative laryngospasm (considered related to implantation procedure and AED treatment; resolved on the same day); fall, convulsion, head injury, and worsened seizures in one subject (considered related to VNS stimulation and AED treatment); and prostatic cancer and suicide attempt in one patient each (not considered related to study treatment). None of the serious AEs reported in the BMP group were considered related to AED treatment. The majority of study discontinuations in either treatment group were due to premature termination of the study by the sponsor (VNS + BMP group: 46/54, 85% and BMP group: 47/58, 81%; data on file at Cyberonics, Inc.). No deaths were reported in this study, and there were no discontinuations due to an AE in either treatment group.

Discussion

This randomized controlled trial—designed to reflect clinical practice—demonstrated that adjunctive VNS therapy after 12-month follow-up is associated with significantly greater improvement in HRQoL over BMP alone (control group) in patients with pharmacoresistant focal epilepsy.

Compared with previous studies assessing long-term outcome of VNS therapy, our study has significant strengths in using a randomized controlled design and a robust primary endpoint such as HRQoL, whose improvement is the ultimate goal of any therapeutic intervention. It is important to note that the study endpoint was determined with an instrument, the QOLIE-89 inventory, which has been validated in many different settings and languages worldwide (including all languages used by our patients) and represents the most comprehensive epilepsy-specific measure of HRQoL currently available.[18] On the other hand, an important study limitation relates to the smaller sample size and shorter duration of follow-up than initially planned. These were a consequence of a low enrollment rate that led to the early study termination by the sponsor. Despite this limitation, and the necessary revision of the statistical plan, the results supported the primary hypothesis by showing significantly greater improvement in HRQoL in patients receiving VNS compared with BMP alone.

The low enrollment rate resulted primarily from the fact that most study candidates had strong views (either positive or negative) about the value of VNS therapy and therefore were reluctant to be randomized. As a consequence, recruited patients are expected to be less biased than those who refused to participate, which might strengthen rather than limit the external validity of a study having quality of life as primary outcome.

It could be argued that because of the open label and flexible design, with individual changes in AEDs possible in both groups, results may have been affected by the patient's or physician's expectations or decisions. Although this limitation is acknowledged, a double-blind design, as well as less flexibility in AED changes, could not be justified for the duration of follow-up required to demonstrate clinically meaningful long-term effects on HRQoL. Indeed, blinding would have required that patients in the control group receive a sham operation or have their VNS device turned off for the entire duration of follow-up, two options that would be difficult to justify ethically. Similarly, flexibility in AED changes in both groups was believed necessary to ensure safe and adequate long-term management of a population with pharmacoresistant focal epilepsy. Furthermore, this flexibility mirrored clinical practice and promoted the external validity of the study. It is notable that our main finding was confirmed after excluding patients from the VNS + BMP group who had changes in their AED treatment.

Changes in AEP scores, which reflect the burden of AED-related toxicity, showed a trend to have a more favorable course in the VNS + BMP group than in the BMP group. This is in contrast with the observation that AEs were reported with a higher frequency among patients treated with adjunctive VNS. This paradoxical finding reflects the fact that patients from the VNS + BMP group filled a specific questionnaire for VNS-related AEs that are not included among the AEP items. Because AED-induced AEs are a major determinant of HRQoL in patients with pharmacoresistant epilepsy,[15,19] the possibility that a reduction in AED toxicity contributed to the better HRQoL outcome in VNS-treated patients needs to be considered. The difference in AEP score changes between the two groups, however, was small and unlikely to account for the significant improvement in HRQoL in the VNS-treated group.

Similar to the trend toward a lower AEP score, the greater seizure reduction in the VNS + BMP group compared with the BMP group might have contributed to the HRQoL benefits associated with VNS. The reduction in seizure frequency in the VNS + BMP group was statistically significant, but of a magnitude that previous studies have shown to affect HRQoL only minimally.[19,20] Moreover, in previous studies, VNS-associated improvement in QOLIE-89 score and other measures of quality of life did not correlate with changes in seizure frequency.[21] Finally, our HRQoL findings do not seem to be primarily driven by an effect of VNS on mood, because no significant differences were observed between VNS + BMP and BMP groups in the two depression scales used in this study (CES-D and NDDI-E), or in the QOLIE-89 Mental Health subscale. Based on these findings, we suggest that the VNS-related improvement in HRQoL in our patients might reflect the sum of modest benefits in multiple factors rather than a single determinant.

The improvement in QOLIE-89 total score and in seizure frequency in the VNS + BMP group compared with the BMP group increased gradually over time and reached a maximum at the end of follow-up (12 months after randomization). However, findings at 3, 6, and 9 months after randomization were not statistically significant, possibly

due to differences in the populations studied at each time point. Yet, these findings are in line with the progressive ramp-up and reported time course of the effectiveness of VNS on seizure frequency,[1,22] as confirmed in this study.

Overall, the results from this trial provide further evidence for the added value of VNS therapy over flexibly adjusted AED therapy in patients with pharmacoresistant focal epilepsy who are not candidates for surgical resection. Moreover, our findings demonstrate that the benefits of such therapy may extend beyond the sole reduction in seizure frequency.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Parameters of VNS pulse generator for patients included in the VNS + BMP treatment group at Months 3 (n = 45), 6 (n = 41), 9 (n = 33), and 12 (n = 28).

Table S2. Change from baseline to Month 12 in QOLIE-89 scores.

Table S3. Change from baseline in QOLIE-89 subscale scores; the number of subjects at each time point for the VNS + BMP and BMP groups, respectively were n = 48 and 48 (at baseline), n = 47 and 47 (at Month 3), n = 38 and 45 (at Month 6), n = 33 and 35 (at Month 9), and n = 31 and 29 (at Month 12).

Table S4. Change from baseline in CES-D, NDDI-E, and AEP scores; the number of subjects at each time point for the VNS + BMP and BMP groups, respectively were n = 48 and 48 (at baseline), n = 47 and 47 (at Month 3), n = 38 and 45 (at Month 6), n = 33 and 34 (at Month 9), and n = 31 and 29 (at Month 12).

Table S5. Antiepileptic drug (AED) treatment and AED load.

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Vagus Nerve Stimulation for the Treatment of Epilepsy

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Epilepsy; Seizures; Epilepsy surgery; Neuromodulation; Vagus Nerve Stimulator

Introduction

About 50 million people worldwide suffer from epilepsy, and about 30 – 40% of these persons have seizures that are refractory to treatment with antiepileptic medication.[2–4] Surgical resection or ablation can result in seizure freedom in well-chosen patients, however, not all persons with epilepsy are candidates for epilepsy surgery.[4] Furthermore, despite careful selection, some patients may continue to experience seizures postoperatively.[5–7] In patients whose seizures are inadequately controlled, neuromodulation based interventions should be considered.[8] Vagus nerve stimulation (VNS) is one of the most common neuromodulation based approaches. The VNS system is a battery powered device that

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resembles a cardiac pacemaker (Figure1). The VNS consists of an implanted pulse generator implanted below the clavicle and lead that is wrapped around the left vagus nerve in the carotid sheath. Although complete seizure freedom with VNS therapy is rare, it may be beneficial in reducing seizure frequency and improving quality of life (QOL).[8]

Several important and early studies of VNS on brain activity were conducted by Bailey and Bremmer in 1938 and by Dell and Olson in 1951.[9–11] These studies proposed that stimulation of the vagus nerve affected cortical activity by way of nucleus tractus solitarii projections to other brainstem nuclei, such as the locus coeruleus and raphe magnus, which project diffusely to the cortex.[9] It has been proposed that VNS exhibits antiepileptic therapy by decreasing interictal events and by desynchronizing cortical activity.[12–14] Zabara additionally showed that anticonvulsant effects of VNS lasted at least four times the duration of stimulation.[13,15,16] Dr. Jacob Zabara and Terry Reese developed the first generation of the vagus nerve stimulator through their newly incorporated company Cyberonics in 1987 (now LivaNova). In 1988, Dr. William Bell implanted the first VNS, the NeuroCybernetic Prosthesis, at Wake Forest University.[9,17] In July 1997, the United States Food and Drug Administration (FDA) approved VNS as adjunctive therapy for adults and adolescents (older than 12 years old) with partial onset seizures that are refractory to antiepileptic medications. More recently, the FDA has expanded VNS approval as an adjunctive treatment in patients 4 years and older with partial onset seizures refractory to medications.[18] Since its original approval over 20 years ago, more than 100,000 patients have been implanted with VNS.[19]

Short term outcomes of vagus nerve stimulation from randomized controlled trials

Efficacy of VNS for the treatment of epilepsy has been examined in four blinded, randomized controlled trials (Class I data), which are summarized in table 1.[20–24] In a 1994 study led by Ben-Menachem et al., 114 patients with partial epilepsy were randomized at multiple centers.[20] These patients received either high-frequency (“therapeutic”) or low-frequency (“sham”) stimulation paradigms. At a three month follow-up, this study reported that high-frequency stimulation reduced seizure frequency by 25% and low-frequency stimulation reduced seizure frequency by 6%. A responder to VNS therapy is commonly defined as seizure frequency reduction by at least 50%, a definition we will use from this point forward.[25] In this study, 31% of patients receiving high-frequency stimulation achieved responder status.[20]

In a subsequent multicenter randomized controlled trial, Handforth et al. randomized 196 patients with partial epilepsy to receive either high-frequency stimulation or sham stimulation.[21] Patients with high-frequency stimulation achieved 28% reduced seizure frequency while those with sham stimulation had a 15% decrease. Overall, 23% of those receiving therapeutic stimulation (high-frequency) achieved responder status at the three month postoperative follow-up. Amar et al. provided further evidence of VNS efficacy with the publication of a randomized controlled trial of VNS implantation in 17 persons resulting in 57% of patients achieving responder status.[22]

In the first randomized controlled trial for children with intractable epilepsy, Klinkenberg et al. randomized patients with partial (N=35) or generalized epilepsy (N=6) to high-output stimulation (maximum 1.75mA) or low-output stimulation (0.25mA) for 20 weeks, followed by an add-on period of 19 weeks of high-output stimulation for all patients.[24] At the end of the randomized controlled blinded period, 16% of patients receiving high stimulation and 21% of patients receiving low stimulation achieved responder status. After the add-on phase, 26% of patients experienced at least 50% reduced seizure frequency.[24] In summary, blinded randomized controlled trials for both children and adults with intractable epilepsy have demonstrated that 23% - 57% of patients typically achieve 50% seizure reduction with VNS implantation in short term follow-up.[20–22,24]

Additionally, these conclusions are supported by two nonblinded randomized controlled trials (Class II data, Table 1) comparing vNs stimulation parameters. The first, a single center study, was conducted by Scherrmann et al. and included 28 patients, and the second, a multicenter study, was performed by DeGiorgio et al. and included 61 patients.[26,27] Scherrmann et al. reported median seizure reduction of 30% and that 45% of patients achieved responder status.[26] DeGiorgio et al. reported a median seizure reduction of 26% and that 29% of patients achieved responder status.[27]

Long term seizure outcomes for VNS from retrospective and prospective cohort studies

Long term studies, including 13 prospective observational studies (Class III data, Table 1), have shown progressive increases in response to VNS with increased duration of implant.[1,23,25] These studies included between 16 and 95 patients and follow- up periods of 3 to 64 months. As seen in table 1, results from these studies report a median seizure reduction rate between 17% - 55% and responder rates between 21% - 54%. To further evaluate VNS response rate over time, one group conducted a review of VNS therapy patient outcome registry data and literature review including 5554 and 2869 patients respectively.[1] From registry data, 49% of patients were responders to therapy and 5.1% of patients were seizure free at zero to four months post-implantation. Subsequently, at 24 – 48 months, 63% of patients were responders with 8.2% achieving seizure freedom. The authors' literary review yielded similar results (Figure 2), with 40% of patients being responders at zero to four months (2.6% seizure free), and 60.1% of patients responded to therapy at last follow-up (8.0% seizure free).[1] It is important to note, however, that these studies are not controlled in nature, and therefore may be susceptible to selection bias, and can overestimate long term favorable outcomes, as patients not receiving response may be less likely to continue therapy.

Quality of life (QOL) outcomes in VNS

The most important predictor for QOL in patients with epilepsy is freedom from seizures.[28] As discussed above, VNS only leads to seizure freedom in about eight percent of patients.[1] Therefore, understanding other QOL outcomes in epilepsy patients with VNS has helped providers to better advise patients about this treatment. One study specifically evaluated QOL metrics in 5000 patients using the VNS therapy patient outcome registry.[29] In general,

this group reported that use of VNS for medically refractory epilepsy was associated with many QOL improvements. However, these findings were based on data subjectively recorded by treating physicians and are therefore susceptible to bias. Specifically, this study reported that patients experienced improvements in alertness (58% - 63%), post-ictal state (55% - 62%), cluster seizures (48% - 62%), mood change (43% - 49%), verbal communications (38% - 45%), school/professional achievements (29% - 39%), and memory (29% - 38%).[29] Additional benefits include reduced sudden unexpected death in epilepsy (SUDEP) rates over time with VNS therapy.[30] Improvements in QOL metrics have been seen in both responders and non-responders, and in adults and children.[29,31] Interestingly, unlike seizure frequency, QOL metrics were not found to improve over time (as seen in figure 3),[29] which may imply that benefit from VNS is not solely due to effects on seizure frequency, or may reflect study bias.

Factors associated with outcome

As with resective surgery, optimal patient selection plays a central role in predicting outcomes of VNS implantation, so understanding factors associated with outcome is imperative.[1,8,32] Currently, VNS is approved as adjunctive therapy in patients four years of age and older with partial onset seizures refractory to medication.[18] Despite the narrow indications for use, VNS has been implemented for treatment of many types of patients with medically refractory epilepsy. A 2015 study of predictors of seizure freedom found that at 4 – 48 months 8.2% of implanted patients became seizure free.[1] Seizure freedom was predicted by age of epilepsy onset > 12 years of age (odds ratio (OR): 1.89 and 95% confidence interval (95CI) 1.01–1.82), and by having a generalized seizure type (OR: 1.38 and 95CI: 1.06 – 1.81). Overall patient response (greater than 50% seizure frequency reduction) was predicted by having non-lesional epilepsy (OR: 1.38 and 95CI: 1.06–1.81) and about 60% all of patients were responders at last follow-up.[1]

Studies of patient groups not included in the original FDA approval (greater than 12 years of age with medically intractable partial epilepsy) have shown that VNS may be beneficial in a wide range of patients with medically refractory epilepsy. An example population that merits consideration are patients with posttraumatic epilepsy (PTE). PTE is a common consequence of traumatic brain injury and accounts for about 20% of symptomatic epilepsy cases.[33,34] These patients are often resistant to treatment with antiepileptic medications and may be unlikely to have a localizable lesion.[35] In a retrospective study, summarized in figure 4, patients with PTE who received VNS achieved greater seizure frequency reduction than patients with nontraumatic epilepsy both at three month follow-up (50% vs 46% fewer seizures) and 24 month follow-up (73% vs 57% fewer seizures).[36] Furthermore, patients with PTE had an overall responder rate of 78% at 24 months versus 61% in the nontraumatic epilepsy group.[36] Additionally, children (< 18 years of age) and patients with less than 10 years of seizures have shown better response to VNS than adults or those with duration greater than 10 years respectively.[23] Another group that has shown favorable outcome with VNS is patients with Lennox-Gastaut syndrome, whose seizure types are typically considered primary generalized.[25,30] These findings indicate that further study of different patient characteristics may yield insight regarding which patients may have greater probability of experiencing a positive response to VNS therapy.

Ictal tachycardia

Modern VNS systems have multiple programming options allowing customization of therapy delivery for individual patients. One common initial programming of VNS stimulation parameters consists of open-loop stimulation cycles of 30 seconds of stimulation every 5 minutes.[37] Additionally, VNS also allows user-initiated stimulation at or before the time of seizure onset with the VNS Manual Magnet Mode.[37] With this manual stimulation initiated by patients or caregivers, some patients may experience benefits such as aborted seizures or decreased post-ictal state.[30,38] However, manual triggering of stimulation may not always be feasible for a variety of reasons, such as lack of premonitory symptoms or seizures in sleep. An automated trigger for stimulation would address some barriers to manual stimulation at time of seizure. Heart rate is an easily measured extracranial biomarker for seizure detection that has been recently implemented into a VNS model.

Ictal tachycardia is defined as increase in heart rate above baseline that is associated with ictal events.[39,40] In a review of 34 articles, Eggleston et al. reported that about 82% of patients with epilepsy experience ictal tachycardia.[40] Furthermore, when examined by seizure type: 64% of generalized seizures and 71% of partial onset seizures were associated with significant heart rate changes.[40] Previous research suggests that propagation of epileptic activity to the right insular cortex may be one mechanism for autonomic nervous system perturbations resulting in ictal heart rate fluctuations.[41] Using this knowledge of ictal tachycardia, the Model 106 VNS Therapy system (LivaNova) includes an automatic stimulation mode (AutoStim) that stimulates the vagus nerve upon detecting tachycardia.[37,42,43]

The efficacy of the AutoStim mode has been studied in two multisite trials: one in the United States (E-37) and one in Europe (E-36).[42,43] Both of these studies defined ictal tachycardia as a heart rate of > 100 beats per minute (bpm) during a seizure, with at least a 55% increase or 35 bpm increase from baseline heart rate.[42,43] The E-37 protocol was a prospective, unblinded United States multisite study of this feature in 20 patients with medically refractory partial onset seizures and history of ictal tachycardia. At 12 months, Fisher and colleagues report that QOL and seizure severity scores may improve with a responder rate of 50%.[42] They noted that during an inpatient observation period, about 43% of all seizures occurred with at least a 20% increase in heart rate compared to baseline heart rate and that complex partial seizures were most likely to be associated with higher heart rate increases.[42] During the E-36 trial, responder rate at 12 months was reported as 29.6%.[43] Extra stimulations triggered by ictal tachycardia did not significantly affect battery life, with measured duty cycles increasing from 11% to 16% with AutoStim activated in the E-37 trial.[42] There are two mechanisms to avoid false positives in the Model 106. First, to avoid false positives due to exercise, AutoStim is triggered by an increase from a baseline heart rate that is continually updated from a moving average. Therefore, while false positive stimulations are possible at the beginning of an exercise session, these should subside once the baseline heart rate is updated to reflect increased heart rate of exercise. Second, a tachycardia detection threshold can be can be customized for each patient as increase from baseline heart rate of 20% - 70%.[37] Additionally, false positive stimulations would not incur any additional risk of adverse events compared to the regularly scheduled stimulations patients receive with

standard open-loop VNS. In summary, ictal tachycardia triggered VNS is at least as effective as standard open-loop VNS and may help abort or reduce severity of seizures in some patients.

Adverse effects and complications

Adverse events associated with VNS fall into two categories: (i) those associated with surgical implantation and (ii) those associated with electrical stimulation.[15] The most common adverse effects of VNS, as summarized by four studies, are shown in table 2.[20,21,24,44] In a recent large retrospective study of 247 primary VNS implants Ben-Menachem and colleagues examined adverse effects specific to the surgical implantation.[45] This group reported a surgical complication rate of 8.6%, with the most common complications being postoperative hematoma in 1.9%, infection in 2.6%, and vocal cord palsy in 1.4% of cases.[45] Across the studies in table 2 and others, hoarseness is the most prevalent adverse effect reported from stimulation.[23] Additionally, asystole or severe bradycardia has been described in very few cases of VNS intraoperatively and postoperatively (0.06 events per 1000 patient years from July 1997 to March 2011).[25,46] Finally, some recent studies have suggested that there may be an association between VNS and sleep apnea, however, the latest American Academy of Neurology guidelines on VNS state that the clinical importance of this effect is still unclear.[30,47]

Non-invasive vagus nerve stimulation

Implantable VNS is a safe and efficacious treatment for medically refractory epilepsy. However, newer non-invasive VNS systems (nVNS) posit to offer the advantage of avoiding most common VNS associated adverse events.[48] The primary advantage of the non-invasive based treatment is avoiding surgery and therefore avoiding implantation associated adverse events such as infection and vocal cord paresis.[49] Additionally, nVNS claims to limit stimulation related adverse events by allowing greater customization of stimulation paradigm.[48] NEMOS (Cerbomed, Erlangen, Germany) is an external transcutaneous VNS available in Germany, Austria, Switzerland, and Italy.[49] NEMOS stimulates the auricular branch of the vagus nerve using an intra-auricular electrode. Patients can control their VNS stimulation during treatment sessions which occur three to four times a day and may each last one to four hours or they may stimulate before a seizure. In a proof of concept trial involving 10 patients with medically refractory epilepsy using one-hour treatments three times a day, five patients reported some seizure frequency reductions, but none achieved 50% reduced seizure frequency.[50] A second non-invasive VNS device is the gammaCore device (electroCore LC. Basking Ridge, NJ, United States of America), which has been studied for patients with chronic headache and migraine but not in patients with epilepsy.[51–53] The gammaCore device is a handheld portable stimulator with two stainless steel round discs that are placed on the skin to deliver electrical stimulation to the vagus nerve. In summary, the advantages of nVNS are they avoid any adverse events associated with surgery for implantable VNS and with less frequent stimulation may reduce the amount of stimulation associated adverse events.[49] However, true efficacy of these nVNS devices has yet to be proven for medically refractory epilepsy, therefore implantable VNS currently remain the superior choice for seizure control.

Future directions for VNS:

Future directions for usage of VNS therapies are extensive. For the first 20 years of its use, VNS was FDA approved only for patients 12 years and older with medically refractory partial epilepsy. However, recent changes have expanded this approval to patients as young as four years old with medically refractory partial epilepsy.[18] As we have discussed above, multiple studies have shown efficacy in patients outside of these categories such as patients with generalized types of epilepsy or non-localizable posttraumatic epilepsy, and future approval for these patients may increase the number of people who benefit from VNS.[1,25,36] Additionally, future VNS systems with closed-loop seizure detection and responsive stimulation may provide additional benefit.[38] These VNS systems may resemble the responsive neurostimulation system (RNS, Neuropace, Mountain View, CA, United States of America). Like the RNS system a closed-loop VNS may offer not only the benefits of seizure onset induced stimulation, but also may also record and provide objective data on seizure frequency to help clinicians accurately assess response to treatment.[54]

Summary / Discussion:

Patients with epilepsy are defined as medically refractory when they have failed to achieve seizure control with two or more antiepileptic medications.[4] These patients should be referred to a comprehensive epilepsy center for surgical evaluation.[8] However, surgery remains underutilized, and on average, patients who are referred have already suffered from 20 years of poorly controlled seizures.[4,55] For patients with certain types of epilepsy, resective epilepsy surgery may result in seizure freedom.[4] Unfortunately, not all patients are candidates for resective surgery. Despite lower rates of seizure freedom, patients who are not candidates for resective surgery should still be offered surgical treatment with neuromodulation techniques, such as VNS therapy. With two to four years of VNS therapy, about 8% of patients will reach seizure freedom, and about 50 – 60% will have at least 50% reduction in seizure frequency.[1] VNS has been used for more than twenty years in clinical practice and serves a vital role for patients with epilepsy who are poor surgical candidates, such as those with generalized or non- localizable epilepsy, and individuals who have failed resection.[1]

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KEY POINTS

- VNS treatment is an efficacious surgical intervention for patients aged 4 years and older with pharmacoresistant epilepsy who cannot receive or failed resective surgery.
- After more than two years of VNS, about 8% of patients achieve seizure freedom, and about 50% will have at least 50% reduced seizure frequency.[1]
- Serious adverse events with VNS, such as device infection, are rare.

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SYNOPSIS

VNS was the first neuromodulation device approved for treatment of epilepsy. In more than 20 years of study, VNS has consistently demonstrated efficacy in treating epilepsy. After 2 years, about 50% of patients will experience at least 50% reduced seizure frequency. Adverse events with VNS treatment are rare and include surgical adverse events (including infection, vocal cord paresis, etc.) and stimulation side effects (hoarseness, voice change, cough). Future developments in VNS including closed-loop and non-invasive stimulation may reduce side effects or increase efficacy of VNS.

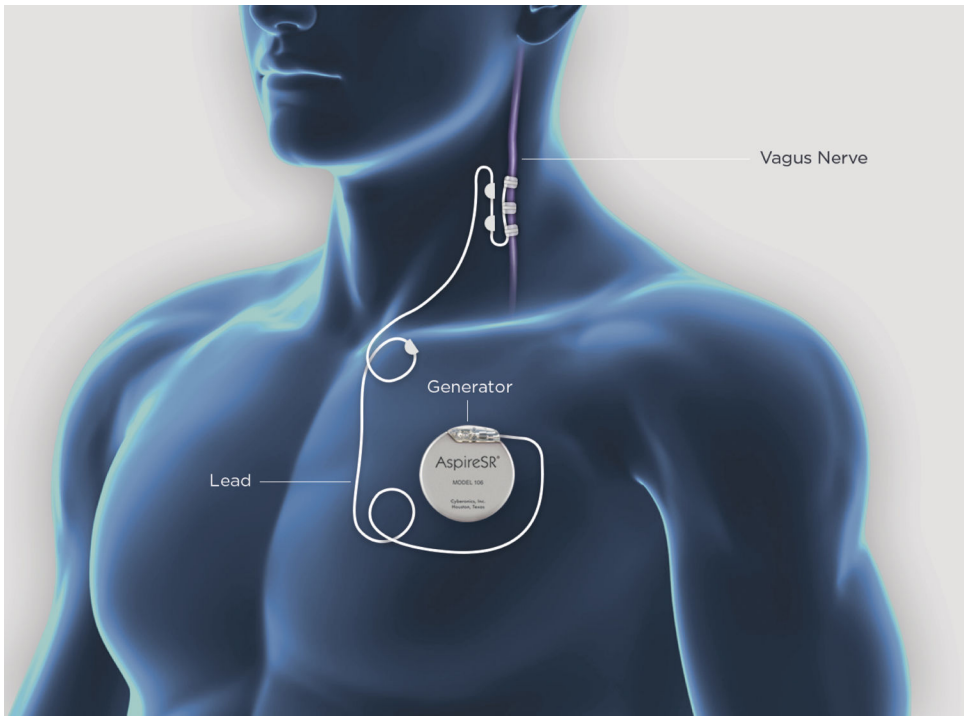

Figure 1. AspireSR® Vagus Nerve Stimulator:
VNS system consists of implanted pulse generator surgically implanted beneath clavicle and lead wrapped around left vagus nerve. *(Courtesy of* LivaNova, Inc. Houston, TX).

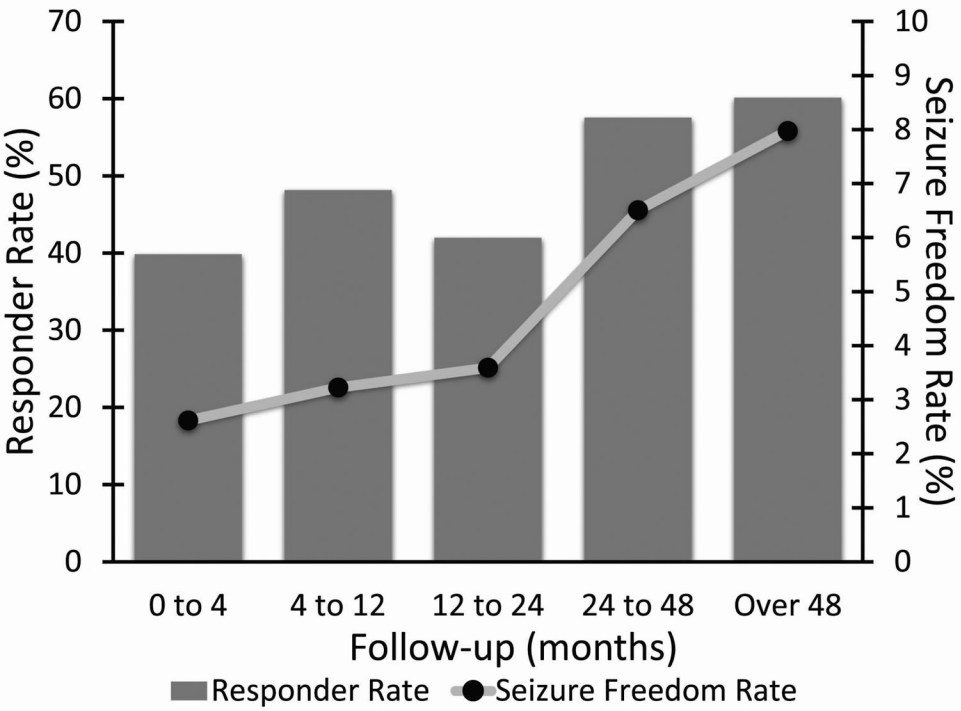

Figure 2. VNS Seizure freedom rate and responder rate from systematic literature review.
This data, from 2869 patients across 78 studies, shows increases in both responder rate and seizure freedom rate over time. At last follow-up 60% of patients achieved responder status to VNS and 8% of patients were seizure free. N = 650, 405, 1503, 876, and 326 patients at each follow-up period, respectively. VNS, vagus nerve stimulation. *(From* Englot DJ, Rolston JD, Wright CW, et al. Rates and predictors of seizure freedom with vagus nerve stimulation for intractable epilepsy. Neurosurgery. 2015;79(3):345–353; with permission.)

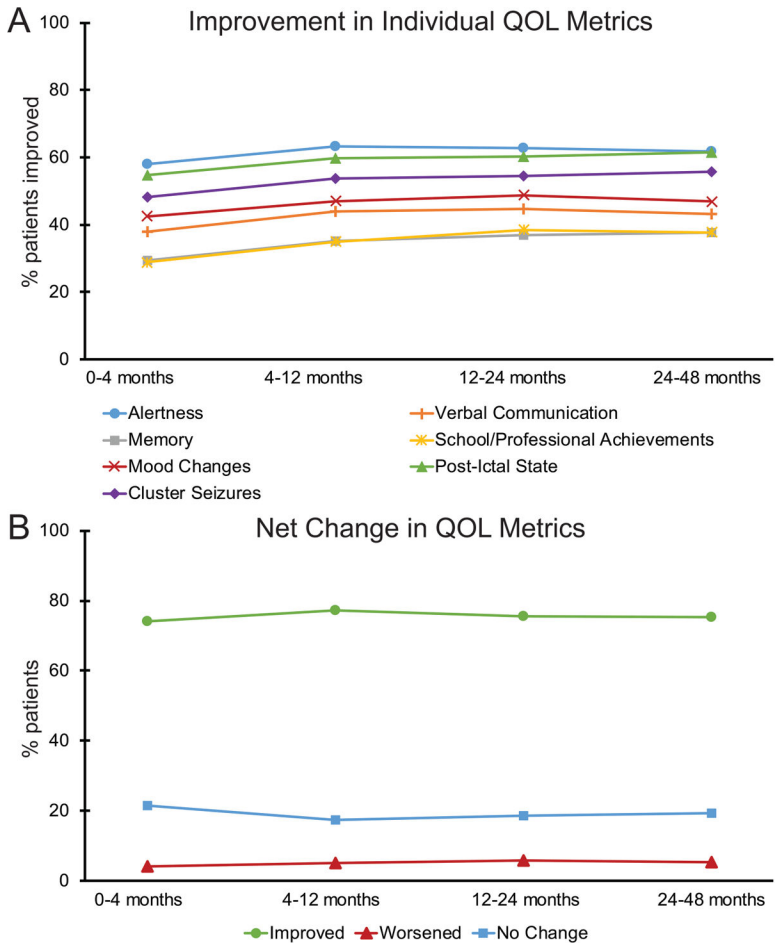

Figure 3. Quality of life metrics for patients with VNS.

(A) When examined individually, multiple metrics of QOL show improvement in patients with VNS as rated subjectively by the treating physician. (B) Overall across all 7 subject QOL metrics there was no trend towards improvement over time with increased time of treatment. For A and B, no significant trends over time were observed ($F < 11$, $p > 0.05$ per metric, Bonferroni corrected). N = 4666 (0 – 4 months), 3277 (4 – 12 months), 3182 (12 – 24 months), and 1194 (24 – 48 months) patients. QOL, quality of life; VNS, vagus nerve stimulation. *(From* Englot DJ, Hassnain KH, Rolston JD, et al. Quality-of-life metrics with vagus nerve stimulation for epilepsy from provider survey data. Epilepsy Behav. 2017;66:4–9; with permission.)

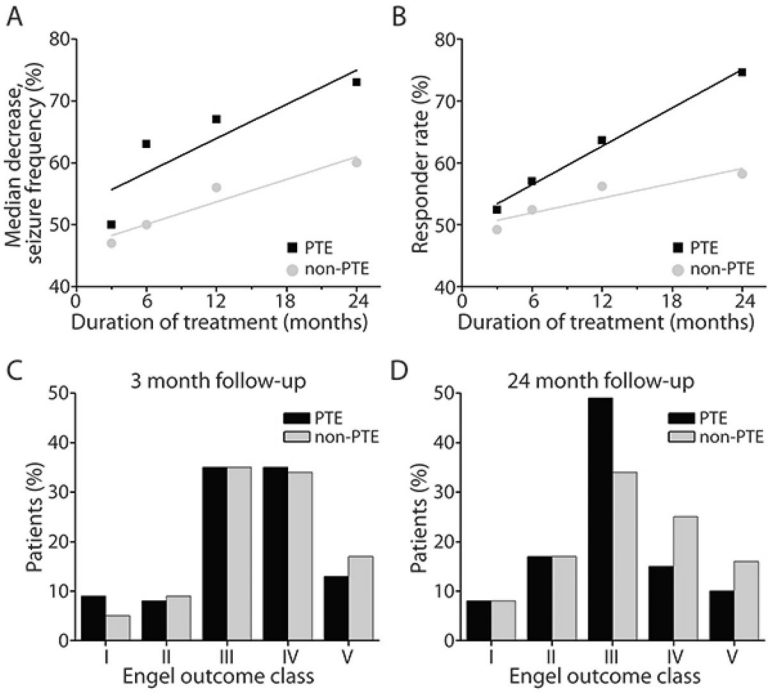

Figure 4. Seizure outcomes after VNS treatment in patients with PTE vs. patients with non postraumatic epilepsy.

The median percent seizure frequency decrease (A) and the responder rates (B) are seen with VNS therapy at 3, 6, 12, and 24 months. Over time, the data shows a trend towards improved seizure outcomes in PTE versus non-PTE patients. When examining Engel outcomes clasess very little difference is found when comparing PTE and non-PTE patients at 3 months after VNS implantation (C). 24 months after VNS (D), patients with PTE exhibit Engel Class III more frequently and Engel Class IV–V less frequently, when compared with non-PTE patients. The number of patients is 254, 158, 154, and 71 for those with PTE and 1449, 975, 878, and 364 for those with non-PTE at 3, 6, 12, and 24 months, respectively. *(From* Englot DJ, Rolston JD, Wang DD, et al. Efficacy of vagus nerve stimulation in posttraumatic versus nontraumatic epilepsy. J Neurosurg. 2012;117(5):970–977; with permission.)

Table 1:
Class I, II, and III evidence of VNS efficacy in epilepsy treatment

Adapted from Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. J Neurosurg. 2011;115(6):1248–1255; with permission.

Class I evidence: Blinded, randomized controlled trials

Study	N	Seizure type	Comparison	Follow-up	No.centers	Mean % seizure reduction	% patients with >50% reduction *
Ben-Menachem, 1994[20]	114	partial	high vs. low stim.	3 months	multi	25 (high) vs. 6 (low)	31
Handforth, 1998[21]	196	partial	high vs. low stim.	3 months	multi	28 (high) vs. 15 (low)	23
Amar, 1998[22]	17	partial	high vs. low stim.	3 months	single	71 (high) vs. 6 (low)	57
Klinkenberg, 2012[24]	41	mixed	high vs. low stim.	3 months	single	16 (high) vs. 21 (low)	26 **

Class II evidence: Non-blinded, randomized controlled trials

Study	N	Seizure type	Comparison	Follow-up	No. centers	Median % seizure reduction	% patients with >50% reduction
Scherrmann, 2001[26]	28	mixed	2 stim. paradigms	NR	single	30 (overall)	45
DeGiorgio, 2005[27]	61	partial	3 stim. paradigms	3 months	multi	26 (overall)	29

Class III evidence: Prospective observational studies (>10 patients)

Study	N	Seizure type	Notes	Follow-up	No. centers	Mean or median % seizure reduction	% patients with >50% reduction
Ben-Manachem, 1999[56]	64	mixed		3 to 64 months	single	NR	45
Parker, 1999[57]	15	mixed	children with encephalopathy	1 year	single	17	27
Labar, 1999[58]	24	gen		3 months	single	46	46
DeGiorgio, 2000[44]	195	mixed		12 months	multi	45	35
Chavel, 2003[59]	29	partial		1 to 2 years	single	53	54 (at 1 year)
Vonck, 1999 & 2004[60,61]	118	mixed		>6 months	multi	55	50
Majoie, 2001 & 2005[62,63]	19	mixed	children with encephalopathy	2 years	single	20.6	21
Huf, 2005[64]	40	NR	low IQ adults	2 years	single	26	28
Kang, 2006[65]	16	mixed	children	>1 year	multi	50	50
Ardesch, 2007[66]	19	partial		>2 years	single	25 (at 2 years)	33 (at 2 years)
Ryvlin 2014[67]	112	partial	VNS+BMP vs. BMP	2 years	multi	23 (at 1 year)	32 (at 1 year)
Fisher 2016[42]	20	mixed	AutoStim trial	1 year	multi	47.3	50
Boon 2015[43]	31	mixed	AutoStim trial	1 year	multi	NR	29.6

* Refers to “high” stimulation group only. NR = not reported.

** Refers add-on period results with all participants switched to high-stimulation.

Table 2:
Incidence (%) of adverse effects of VNS for epilepsy

Adapted from Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and preictors of response. J Neurosurg. 2011;115(6):1248–1255; with permission.

no. patients follow-up	Ben-Menachem, 1994[20] 114 3 months	Handforth, 1998[21] 196 3 months	DeGiorgio, 2000[44] 195 1 year	Klinkenberg 2012[24] 41 3 months
Hoarseness	37	62	55	19.5
Cough	7	21	15	7.3
Paresthesia	6	25	15	4.8
Pain	6	17	15	7.3
Dyspnea	6	16	13	NR
Headache	2	20	16	2.4
Infection	NR	4	6	4.8

NR = not reported.

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Clinical outcomes of closed-loop vagal nerve stimulation in patients with refractory epilepsy

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ABSTRACT

Purpose: The AspireSR® is a vagal nerve stimulation (VNS) device that operates as a closed-loop system, delivering an automatic stimulation in response to an ictal heart rate increase that serves as a predictor for an imminent seizure.

Our purpose is to assess the outcome of the AspireSR® in a patient population managed in a pediatric neurology unit.

Methods: The records of patients who underwent transplantation during 2015–2017 and are continuously followed in one pediatric-epilepsy clinic, were retrospectively analyzed. Collected information included demographics, use of antiepileptic drugs and seizure type, frequency and duration before and after VNS implantation.

Results: 46 patients ages 5–31 years (mean 15.7 ± 5.8), mean age at implantation 14 ± 5.8 years, were included. 29 patients (63%) were new insertions and 17 of the patients (37%) underwent a VNS replacement to the AspireSR® model. Mean follow-up was 13 ± 7.5 months (range 2–29 months). The total cohort responder rate (patients with ≥50% reduction in seizure frequency compared to the pre-implantation period) was 60.9%. (62% in the new insertion group; while 59% in the replacement group had additional benefit over their former VNS model, p = 0.981). Epilepsy etiology, age, age at implantation and type of seizures pre-implantation showed no correlation to response-rate. Five patients (10.9%) experienced complete seizure-freedom following implantation (4/5 in the "new insertion" group). Responses were reported at median follow up of 5 ± 1.3 months post-implantation. 67.4% experienced shorter seizure duration post-implantation.

Conclusion: Our results suggest that the AspireSR® device provides an early and meaningful benefit to drug-resistant epilepsy patients, which is relevant for both patients with new insertions and those with replacements of former VNS devices.

1. Introduction

Epilepsy is a group of neurological disorders characterized by recurrent epileptic seizures with a prevalence rate of 0.5%–1% among children [1]. Most patients are successfully treated with anti-epileptic drugs, but about a third suffer from treatment-resistant epilepsy (TRE) [2]. Vagal nerve stimulation (VNS), approved by U.S Food and Drug Administration (USFDA) in 1997, is a safe and efficacious treatment for TRE, consisting of an implanted pacemaker-like generator and nerve stimulation electrodes, that delivers intermittent stimulation to the patient's left vagus nerve [2]. The indication for use of VNS outside of the U.S. is as an adjunctive therapy for reducing the frequency of seizures in TRE patients whose epileptic disorder is dominated by partial or generalized seizures once resective surgery is deemed not a viable option [3]. The mechanism of effect of VNS is currently unclear, but several pathways have been proposed and studied so far, including an increase in the release of neurotransmitters, such as norepinephrine and serotonin, increased cerebral blood flow to the thalamus and cortex and desynchronization of the alpha rhythms, as observed on EEG [4].

The first model of VNS device delivered stimulation in an open-loop fashion, consisting of continuous ON-OFF cycles with an on-demand stimulation magnet allowing patients and their caregivers to interrupt seizure activity by passing a hand-held magnet over the implanted device [5]. The reported responder rate of the open-loop VNS treatment

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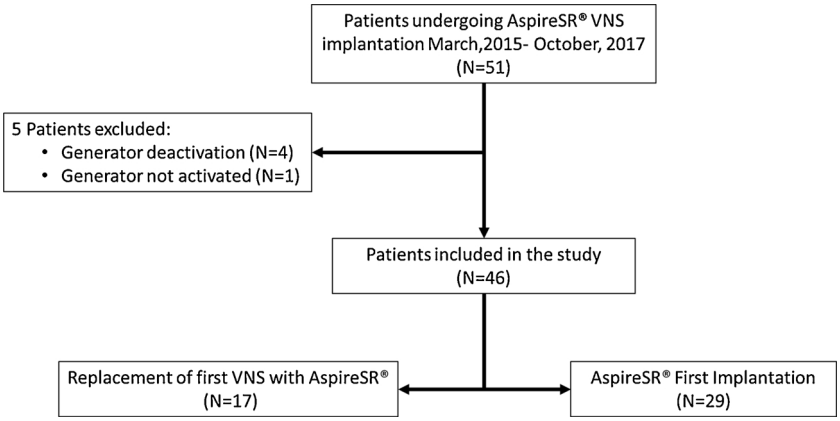

Fig. 1. Study flow chart.

varies between different studies, but according to a research done on 347 children, stands at 43.8% [6]. Elliott et al. have found VNS efficacy to be highest in patients suffering from partial seizures [2]. As for the magnet on-demand stimulation, it resulted in complete termination of seizures in 16.1% of children and adolescent patients, and a partial effect in 73.2% of them [7].

In 2015, based on observations that 82% of epileptic patients present ictal or pre-ictal increases in heart rate (HR), a novel cardiac-based seizure detection algorithm was developed and incorporated into a new VNS model – VNS AspireSR® (SR - seizure response). The AspireSR® provides, in addition to the standard open-loop VNS features, an additional automatic vagal stimulation which is triggered in response to ictal HR increase of at least 20% and delivered in a closed-loop fashion [5]. In the E-36 study, a prospective study conducted by Boon et al, on 31 adult patients (ages 19–66 years), the sensitivity of HR-increase detection of this new model was found to be above 80% for at least one of the algorithm settings, and the automatic stimulation has immediately terminated 58.8% of the seizures [5]. It should be noted that the algorithm is designed to detect rapid HR changes, and thus, it distinguishes the dynamics of HR-increases associated with seizure activity from those associated with physical activity. Of all seizure types, focal onset seizures with impaired awareness were found to be more likely to be associated with higher HR-increases [9]. Furthermore, it has been found that earlier automatic stimulation following the ictal HR, was correlated with shorter duration seizures [10].

The U.S. E-37 trial, was one of the first studies performed to evaluate the AspireSR® clinical outcomes. It recruited 20 adult subjects (ages 21–69) with drug-resistant partial onset seizures and a history of ictal tachycardia. The study has found the responder rate to be 20%, 35%, and 50% at 3, 6, and 12 months follow-up respectively, higher than those reported following standard VNS therapy [9]. Seizure severity rated on a physician-scored severity scale as well as reported by patients and caregivers was significantly reduced at all three follow-up periods. Additionally, several quality of life indicators in epilepsy such as cognitive function and seizure worry showed significant improvement compared to baseline.

The aim of our study was to assess the long-term outcomes of AspireSR® therapy in a real-world patient population managed in a pediatric neurology unit. We describe findings from a retrospective cohort study performed in order to further understand the AspireSR® therapy effects on seizure profile.

Our primary objective was to examine the responder rates following implantation. We further sought to determine whether reduction of seizure frequency occurs with AspireSR® earlier post insertion than with the standard open-loop model VNS. An evaluation of a subgroup of patients who underwent open-loop VNS to AspireSR® replacement is also presented.

2. Materials and methods

2.1. Eligibility criteria

The study included patients that were referred to VNS AspireSR® implantation from the Pediatric Neurology Unit at Chaim Sheba Medical Center between March 2015 and October 2017 (N = 51). Indications for VNS implementation were resistance to ≥3 anti-epileptic medications in patients which were not considered appropriate candidates for epilepsy surgery. The indication for replacement of a previous VNS was insufficient reduction in seizure frequency with the existing devise, or in patients who approached battery expiration time. Eligibility criteria for the study included a minimum of 4 months of follow-up following device activation for naïve patients (patients whose closed-loop VNS was their first device), whereas those who had their VNS replaced, were eligible immediately following implantation. Five patients were excluded from the study, four of them due to generator deactivation, and one whose generator was never activated.

In total, 29 patients (63%) were first insertions and 17 patients (37%) underwent a VNS replacement to the new AspireSR® model (Fig. 1, Flow chart).

2.2. Device parameters

AspireSR® parameters were adjusted by the primary epileptologist during the follow-up according to a formal protocol, until steady therapeutic parameters were achieved (Table 1). For duty cycle, the mean was 20.2 ± 9.8% ON time, mean AC output current was 1.4 ± 0.55 mA. The means were calculated for parameters derived

Table 1
: Programmed device parameters.

Duty Cycle	% ON Time	N (%)
	10	16 (34.8%)
	15	1 (2.2%)
	16	15 (32.6%)
	25	10 (21.7%)
	35	4 (8.7%)
AC	**Output Current (mA)**	
	0.5	1 (2.2%)
	1.3	2 (4.3%)
	1.5	28 (60.9%)
	1.8	14 (30.4%)
	1.9	1 (2.2%)
Sensitivity	**Heart Rate Increase (%)**	
	20	30 (65.2%)
	30	14 (30.4%)
	40	2 (4.3%)

from the programmers at the Pediatric Neurology unit. In 65% of patients, device was set to a threshold of 20% increase in HR, in 30.4% of patients to 30% increase in HR and in 4.3% of patients to 40% increase in HR.

2.3. Study design

This was a retrospective cohort study. Data were collected on December 2017 from the computerized medical record system of Sheba Medical Center. Seizure frequency and duration data were obtained by reports from patients and caregivers, for the period following completion of device-adjustment/tuning. For patients who replaced a former standard VNS device with the AspireSR®, baseline was defined as the period following implantation of the original VNS device. Categories of reduction of seizure frequency following AspireSR® VNS implantation were: 25%, 50%, 75% reduction or complete seizure-freedom. The primary objective was the responder rate, the proportion of patients who experienced ≥ 50% seizure frequency reduction. Any patient who experienced ≥25% seizure frequency reduction was considered to have benefited from the AspireSR®. For this population, time to onset of frequency reduction was measured in months.

2.4. Statistical analysis

Categorical variables were described as frequency and percentage. Continuous variables were evaluated from normal distribution using histogram and reported as median and interquartile (IQR) range. Kaplan-Meyer curve was used to describe improvement during follow-up time. Mek-Nemar test was used to compare the duration of seizures between the periods prior to and following implantation. Mann-Whitney test was used to compare ordinal and continuous variables between implantation and re-implantation. Categorical variables were compared between implantation and re-implantation using Fischer exact test or Chi-square test. Etiology frequency was calculated by Kruskal-Wallis test. Seizure type was analyzed by Mann-Whitney test.

All statistical tests were two-tailed and p-values < 0.05 were considered as statistically significant. SPSS software was used for all analyses (IBM SPSS Statistics, version 23, IBM Corp., Armonk, NY, USA, 2015).

3. Results

3.1. Study population

The study was conducted at a pediatric neurology unit; however, 14 (30%) of the patients continued their follow-up and management in the unit into their adulthood (mainly those suffering from intellectual disability). Therefore, the analyzed cohort was comprised of 46 patients ages 5–31 years (mean 15.7 ± 5.8 years) of whom 30 (66%) were ≤18 years old. The mean age at implantation was 14 ± 5.8 years. There was no statistically significant difference between the first implantation and the VNS replacement cohorts in age, age at implantation, etiology of epilepsy or type of seizures. 52% of the patients (n = 24) suffered from intellectual disability. Mean follow-up was 13 ± 7.5 months (range 2–29 months). The demographic and clinical characteristics of the study population are presented in Table 2.

Mean number of anti-epileptic drugs (AEDs) failed prior to the implantation among patients was 4 ± 1.5. Patients were classified according to seizure types reported prior to the AspireSR® implantation; patients with several types of seizures could belong to more than one group. Sixty one percent of the study population reported Generalized Onset Seizures (Table 2).

3.2. Rate of responders

In total, after a mean follow-up of 13 months, the responder rate (patients with ≥50% reduction in seizure frequency) was 60.9% (28 patients) (Table 3). Five patients [10.8% of cohort] (of whom 4 had their first implantation) were seizure-free following the AspireSR® treatment. In addition, 31 patients (67.4%) experienced shortening of seizure duration following AspireSR® implantation.

Among patients for whom the AspireSR® was the first VNS, the responder rate was 62%. Among those who replaced a previous VNS with the AspireSR®, 59% experienced ≥50% reduction in seizure frequency compared to the period with the former VNS (p = 0.981).

Table 2
: Demographic and Clinical Characteristics of Study Population.

Variable		
Children (< 12 years) N (%)	13 (28%)	
Children (< 18 years) N (%)	30 (65%)	
Adults N (%)	14 (30%)	
Age mean (range)	15.7 (5-31)	
Age at VNS Implantation mean (range)	14 (4-29)	
VNS Replacement N (%)	17 (37%)	
Intellectual Disability N (%)	24 (52%)	
Prior epilepsy Brain Surgery N (%)	3 (7%)	
Etiology N (%)		
	Genetic	14 (30.4%)
	Immune	6 (13%)
	Infectious	1 (2.2%)
	Structural	10 (21.8%)
	Unknown	15 (32.6%)
No. of Failed Anti-Epileptic Drugs N (%)		
	2	3 (6.5%)
	3	5 (10.9%)
	4	8 (17.4%)
	5	7 (15.2%)
	6	23 (50%)
No of Failed Ketogenic Diet N (%)		10 (21.7%)
No of Failed CBD N (%)		17 (37%)
Types of seizure	Generalized Onset Seizures	61%
	Focal Onset with Impaired Awareness	25%
	Non motor Seizure	13%
	Myoclonic Seizures	4%
	Focal Onset Seizures	2%

Table 3
: Rates of Response (Reduction in Seizure Frequency).

Categories of Reduction* in Seizure Frequency	N (%)
No reduction	13 (28.3%)
≥25%	33 (71.7%)
≥50%	28 (60.9%)
≥75%	18 (39.1%)
Complete elimination of seizures	5 (10.9%)

* Compared to the Period preceding the AspireSR device implantation.

3.3. Time to response onset

Time to response onset, analyzed with the Kaplan-Meier method, is presented in Fig. 2. 65% of the patients responded within the first 6 months following AspireSR® implantation. Median time to improvement was 5 ± 1.3 months. Statistical analysis revealed no effect of etiology of epilepsy or type of seizure on time to response.

Seizure reduction was first noticed within 3 months after implantation in the majority of the VNS replacement cohort (53%), as compared to 6 months or less for most of the first implantation cohort (55%). Mann-Whitney test revealed that those who underwent VNS replacement to AspireSR® responded significantly faster after device activation (shorter onset period), than patients who had their first implantation (p = 0.028). Nevertheless, the responder rates at the end of

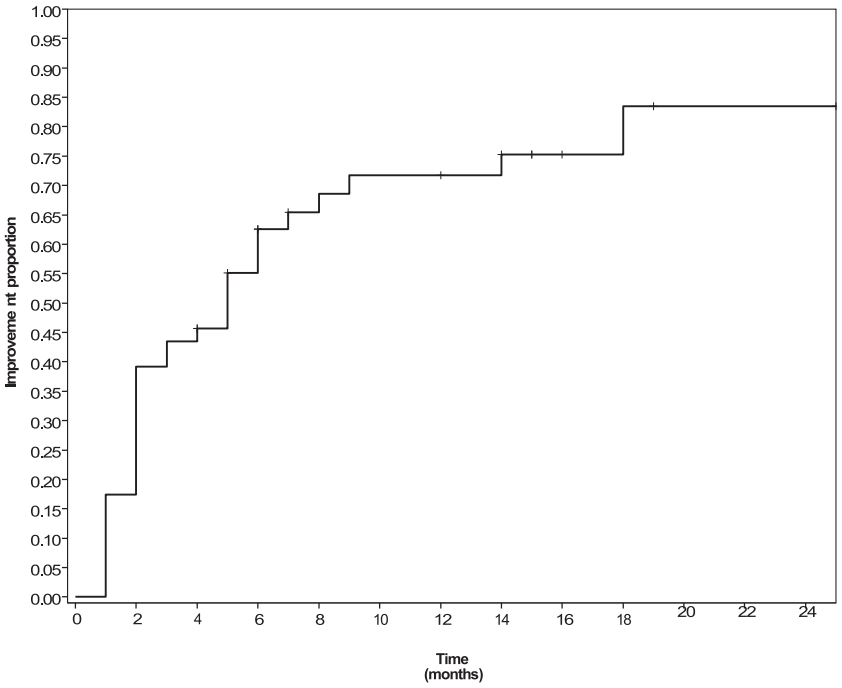

Fig. 2. Time to response.

follow-up were similar across the two cohorts (62% for the VNS replacement group vs. 59% for the first implantation group).

4. Discussion

In this study, we retrospectively analyzed the efficacy of AspireSR®, a VNS device that operates as a closed-loop system, delivering an automatic vagal stimulation in response to an ictal HR increase of at least 20% that serves as a predictor for an imminent seizure [5]. The responder rate in our population was 60.9%. In this cohort of patients with severe epilepsy, resistant to multiple anti-epileptic drugs, 5 patients (10.9%) became seizure-free following implantation, providing strong evidence for the efficacy of the therapy. In addition, 67.4% of patients experienced shortening of seizure duration.

Among the first-insertion cohort, 62% were responders, and 59% of patients who replaced a previous VNS with the AspireSR®, experienced ≥50% reduction in seizure frequency on top of any benefit provided by the former VNS. This is of specific importance showing the added value of the AspireSR® device over the previous open loop model especially when taking into account that patients who agreed to replace a VNS with a newer model are most likely those who have experienced improvement with their previous one.

In our study, improvement was observed early, at a median follow-up time of 5 months, and a responder rate of 60.9% was achieved after a maximal follow-up of 29 months. Response was achieved faster among the replacement cohort than the new-insertion cohort, suggesting a potential cumulative effect. The rapid, relatively high rates of response and seizure freedom in our cohort may be attributed to the higher device sensitivity threshold that we used. At the end of the device ramping-up period, < 5% of the study population remained with our initial device setting of a threshold to 40% increase in heart-rate. Close to 95% of devices were set to a threshold of 20–30% increase in ictal HR. The increased sensitivity of the Auto-Stimulation was not accompanied by elevated rates of adverse effects. Moreover, in none of the patients worsening of seizures was reported after implantation.

A few studies have retrospectively analyzed the data of pediatric drug-resistant epilepsy patients, following the implantation of a standard open-loop VNS. Elliott and colleagues evaluated 141 consecutive cases and found a response rate (≥50% reduction in seizure frequency) of 64.8%, of which 41.4% of patients reported a reduction of ≥75% [2]. Orosz and co-authors analyzed the data of 347 cases and found responder rates of 32.5%, 37.6%, and 43.8% at 6, 12, and 24 months after implantation, respectively [6]. Majkowska-Zwolińsk and group have analyzed the data of 57 cases, and found responder rates of 46.4%, 50% and 55.6% at 6, 12, and 24 months [7]. The difference in responder rate between these studies may be correlated to the differences in follow-up periods, as response to VNS has been found to increase progressively with time [11]. In the Elliott study, the mean duration of VNS therapy was 5.3 ± 3.1 years for the entire cohort (range 25 days–11.4 years), compared to a maximal 2 years in the Orosz and Majkowska-Zwolińsk studies. The positive effect that we observed in our patients with the closed-loop VNS was obtained sooner: response was observed at a median follow-up of 5 months post-implantation.

In our study, 62% of patients for whom the AspireSR® was the first implanted VNS device were responders. This result is in line with a recently-published study conducted in adults with the same device and same mean follow-up time (13 months) by Hamilton and colleagues [12]. These authors showed a 59% (N = 30) response-rate among patients for whom the AspireSR® was the first implanted VNS ("new-insertion cohort", N = 51). In the Hamilton study, the replacement group responders rate increased from 53% (patients with ≥50% reduction in seizure frequency compared to the pre-implantation period) to 71% demonstrating a 32% additional benefit with the AspireSR. Whereas in our population, the additional benefit for the replacement cohort was 59%.

Hamilton and colleagues reported a 6% (3 patients) seizure-freedom among the new-insertion cohort, whereas in our new-insertion cohort, the rate of seizure-freedom was 13.8% (4 patients). In the future, as more experience with the AspireSR® will be accumulated, it will be possible to reach more accurate characterization of the specific populations and treatment settings that will lead to maximal benefit from the device. In our sample, most patients were children, and no significant differences were found between patients over 18 years of age and pediatric patients. Hamilton's study recruited only adults. Taken together, results of the Hamilton study and ours suggest that the benefit of the AspireSR® is relevant for a wide range of patient ages.

In our sample, 13 patients (28.3%) reported ≤ 25% reduction in seizure frequency following implantation of the AspireSR® and no patients reported worsening in seizure frequency. By comparison, in the Orosz study with the standard open-loop VNS, 136 patients (39.3%) had a ≤ 25% reduction in seizure frequency and an increase in seizure frequency was reported in 21 patients (6.1%) [6]. At 24 months of follow-up, Majkowska-Zwolińsk reported no effect of the VNS on seizure frequency in 12 patients (22.2%) [7]. These sub-groups seem to represent a patient population with extremely refractory disease, unresponsive to therapy. Among our patients who experienced ≤ 25% reduction in seizure frequency, 9 patients (31% of the cohort) were new-insertions, and 4 patients (23.5% of the cohort) were replacements. These rates are higher than observed in the Hamilton study (10% in new-insertions and < 2% in replacements). Further research is needed to ascertain the underlying reason for these differences that may include differences between adult and pediatric epilepsy populations or differences in follow-up period between the studies.

Our study was limited by the small sample-size and by its retrospective design. We evaluated the efficacy of the device based on medical records and retrospective interviews with patients' care-givers. This type of design predisposes data to biases, including recall-bias of the care-givers as well as selection bias resulting from lack of randomization. Moreover, data was available from routine clinic visits, which differ in number between patients, and not pre-planned, at the same time intervals. Large-scale prospective studies, using standardized seizure-information collection methods and device management data, can provide a more accurate estimate of the device efficacy and overall effect on patient well-being.

In conclusion, our results suggest that the closed-loop AspireSR® VNS device provides a benefit to drug-resistant epilepsy patients managed in a pediatric and young adults neurology unit once resective surgery is deemed not a viable option, with a responder rate of 60.9% of the study population. The benefit was observed both in patients for whom this was the first implanted VNS and those for whom the AspireSR® was a replacement for a previous VNS. Complete seizure freedom was achieved in 13.8% of new-insertions and 10.8% of complete cohort. Response was achieved rapidly, with a median of 5 months post-implantation, potentially due to the use of threshold to as low as 20% increase in ictal HR. This increased sensitivity setting did not cause elevation in adverse event rates. Should this connection be corroborated by larger-scale prospective studies, it can direct physicians to choose a setting of higher sensitivity to HR increases in most patients, in pursuit of better results.

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Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REVIEW
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Responsive Vagus Nerve Stimulation for Drug Resistant Epilepsy: A Review of New Features and Practical Guidance for Advanced Practice Providers

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Vagus nerve stimulation (VNS) is a safe and effective therapy that has been available for over 20 years for adults and children with drug resistant epilepsy (DRE). Since U.S. Food and Drug Administration approval in 1997, VNS has been implanted in over 100,000 patients including over 30,000 children as an adjunctive therapy in reducing the frequency of seizures in patients 4 years of age and older with focal seizures that are refractory to antiseizure medications. VNS Therapy® has evolved over time and currently offers closed-loop, responsive stimulation as well as advanced features that streamline dosing and patient management. Advanced Practice Providers (APPs) such as nurse practitioners, physician assistants and clinical nurse specialists are integral in a comprehensive healthcare team, and dedicated VNS clinics have formed at comprehensive epilepsy centers across the world that are often managed by APPs. This approach improves access, education, and continuity of care for those with VNS or those considering VNS. Here we provide a review for APPs on the VNS Therapy® system focused on new features, dosing, and troubleshooting strategies with the goal to provide guidance to those managing VNS patients.

Keywords: VNS Therapy®, neuromodulation, closed-loop stimulation, dosing, programming

INTRODUCTION

The field of bioelectric neuromodulation is growing as a complementary intervention to pharmaceuticals. While pharmaceuticals deliver a dose of small molecules that are circulated throughout the body, neuromodulation devices deliver targeted doses of electrical stimulation to the body's neural circuitry which can be implemented to treat a wide array of disorders. New terms for this field such as bioelectric medicines and electroceuticals highlight the similarities between neuromodulatory and pharmaceutical interventions. Despite these similarities, neuromodulation offers key advantages in terms of reversible, targeted therapy with minimal long-term side effects and adherence issues.

Communication in the form of electrical signals travels bidirectionally between the peripheral and central nervous system with the vagus nerve being one of the largest and longest transmission lines connecting much of the body's internal organs to the brain. Therefore, it is no surprise that modulation of the vagus nerve is the most studied and targeted peripheral nerve in the field of neuromodulation. In the past decade, over 2,500 articles on vagus nerve stimulation (VNS) have been published, and VNS has been investigated in a wide range of disorders including epilepsy, depression, heart failure, stroke, tinnitus, inflammation, and more.

Vagus nerve stimulation therapy received U.S. Food and Drug Administration (FDA) approval as an adjunctive treatment for drug resistant epilepsy (DRE) in 1997 as well as treatment resistant depression in 2005. Over the past two decades, VNS Therapy® has been implanted in over 100,000 people with DRE, and a large breadth of evidence has since formed confirming the safety and efficacy of VNS in DRE. Neuromodulation therapies have been on the rise, and VNS Therapy® for DRE has evolved into a smarter and more versatile therapy. Patients and healthcare providers can now benefit from closed-loop, responsive VNS and advanced features that enable more personalized therapy and streamlined dosing.

Vagus nerve stimulation clinics have formed at epilepsy centers across the world which counsel, manage and treat DRE patients with VNS as well as DRE patients that may benefit from VNS. Advanced Practice Providers (APPs), which includes nurse practitioners, physician assistants and clinical nurse specialists, have become increasingly integral in the delivery of neurological care (1) including that in epilepsy (2). Advanced Practice Providers often play a key role in VNS clinics by improving access and promoting continuity of care through patient and family education, managing patient therapy and providing essential follow-up care to VNS patients. Kennedy and Schallert published a nursing review on VNS in 2001 summarizing VNS Therapy®, guiding nurses in the daily treatment of patients with VNS devices (3). This article provides an update on the Kennedy and Schallert nursing review by detailing the approach to a dedicated VNS clinic, a discussion of the closed-loop nature of VNS including improved understanding of dosing, advanced features, and troubleshooting techniques that aid in improved patient management by APPs practicing in epilepsy clinics. The goal is to provide guidance to APPs new to VNS Therapy® as well as those already managing VNS patients or clinics.

TRADITIONAL VNS

The VNS Therapy® system includes a pulse generator surgically implanted below the left clavicle which connects to a wired lead that is tunneled to the neck and terminates with electrodes wrapped around the left cervical vagus nerve. The generator sends electrical pulses through the lead and electrode to the vagus nerve. The goal of electrical stimulation is to activate vagal afferent fibers that project to the nucleus tractus solitarii (NTS) which sends signals to other brainstem nuclei including the raphe nucleus (serotonergic neurons) and locus coeruleus (noradrenergic neurons). Neuromodulation of electrical and chemical signaling through these brain regions is thought to be responsible for the anti-seizure effect of VNS (4).

Traditional VNS includes two modes of stimulation: normal mode (open-loop) and magnet mode (on-demand). Normal mode stimulation is the primary operating mode in which the device continually cycles between on and off periods (e.g., 30 s on and 5 min off). Magnet mode stimulation allows the patient or caregiver to deliver on-demand stimulation triggered by swiping a magnet over the area of the implanted pulse generator.

Five clinical trials (E01–E05) evaluating traditional VNS were conducted between 1988 and 1997 which enrolled a total of 454 patients with DRE. The two randomized, blinded, active controlled trials, E03 and E05, compared a cohort receiving traditional VNS (high-stimulation group) to a cohort receiving presumably subtherapeutic VNS (low-stimulation group). After 3 months, the high-stimulation group had a significantly higher mean seizure frequency reduction than the low-stimulation group [24.5 vs. 6.1% in the E03 trial (5) and 27.9 vs. 15.2% in the E05 study (6)]. Long-term, open-label follow-up of the subjects enrolled in the E01–E05 clinical studies showed seizure reduction continued to improve over time with mean seizure frequency reductions of 44% after 2–3 years of VNS Therapy® (7).

More recently, a retrospective analysis of 436 patients treated with traditional VNS showed a mean seizure reduction of 55.8% after a mean follow-up of 5 years (8). Of those patients with > 10 years of follow-up ($n = 65$), seizure-reduction continued to improve with follow-up duration to 75.5% after 8 years (9). A systematic review of 2,869 patients across 78 studies and VNS registry data from 5,554 patients, revealed ∼60% of patients achieved a ≥50% seizure reduction after 2–4 years, with a seizure-freedom rate of 8% (10).

In addition to improvements in seizure control, VNS has shown to improve quality of life. In the VNS Therapy Patient Outcome Registry, quality of life metrics were assessed by providers in over 5,000 patients at various follow-up visits. Providers reported improvements in alertness (58–63% of patients, range over follow-up period), post-ictal state (55–62%), cluster seizures (48–56%), mood change (43–49%), verbal communication (38–45%), school/professional achievements (29–39%), and memory (29–38%) (11). Reports of improvements in mood associated with VNS (12, 13) led to the investigation of VNS in treatment resistant depression (14) which was later FDA approved in 2005.

MODERN VNS

Acute benefits of on-demand VNS were observed by manually swiping a magnet over the pulse generator prior to or during a seizure (15). Therefore, closed-loop or responsive VNS was developed to automatically deliver VNS in the absence of the ability to perform a magnet swipe. Since ∼82% of people with epilepsy experience increased heart rate during seizures, defined as ictal tachycardia (16), a cardiac based seizure detection algorithm was implemented. Although this detection system does not have the ability to identify ictal events, it uses heart rate

increases as a surrogate marker for seizures. This third mode of VNS is known as AutoStim and is available with generator models 106 AspireSR® and 1000 SenTiva®.

AutoStim was first clinically evaluated with the model 106 AspireSR® generator in a multicenter E-36 study in Europe (17) and E-37 study in the United States (18). Combined, 51 patients were implanted with VNS and observed in the epilepsy monitoring unit with AutoStim enabled. A total of 155 seizures were recorded from 32 patients. AutoStim was triggered during 48 of the 155 (31%) seizures. During the period of AutoStim being delivered, 29/48 (60%) of seizures ended. Responder rates at 12 months were 30% (8/27) in the E-36 study and 50% (10/20) in the E-37 study.

The AutoStim feature works by comparing the heart rate over the last 10-s (foreground) with the heart rate over the previous 5-min (background). Triggering of AutoStim occurs when the foreground heart rate exceeds the background heart rate by a programmer-defined threshold which can be set between 20 and 70% in 10% increments. The AutoStim threshold setting impacts the sensitivity of triggering an automatic stimulation based on heart rate changes, the rate of nonseizure-related automatic stimulations, and latency in triggering stimulation relative to the seizure onset. The lowest AutoStim threshold of 20% is associated with the highest sensitivity, capturing ∼80% of seizures, and highest false positive rate of ∼7 nonseizure-related stimulations per hour. The AutoStim feature is designed to limit the patient from getting stimulation at an unsafe duty cycle. As AutoStim threshold increases, sensitivity decreases as well as the number of false positives. Data from the E-36 and E-37 studies showed that lower AutoStim thresholds corresponded to shorter latency between seizure onset and triggering of AutoStim, and shorter latencies were associated with shorter seizure durations. Therefore, lower AutoStim thresholds have the potential to detect more elevations in heart rate associated with seizures with an earlier response time but also deliver more nonseizure-related stimulations which will increase the overall duty cycle (19). In the E-37 study, AutoStim was associated with a 5% increase in duty cycle (11% without AutoStim compared to 16% with AutoStim) (18).

Five separate studies (20–24) reported long-term outcomes in patients starting on AutoStim, either via a new VNS implant or a replacement with an AutoStim capable generator. Combining these datasets resulted in 80 patients who received new VNS implants and 151 patients receiving a generator replacement. Sixty percent of patients newly implanted with AutoStim VNS enabled were considered responders with a ≥50% reduction in seizure frequency after a mean follow-up period of 13 months. For those on traditional VNS receiving a generator replacement with AutoStim enabled, more than one-third of patients experienced additional improvement in seizure frequency by adding AutoStim (**Figure 1**).

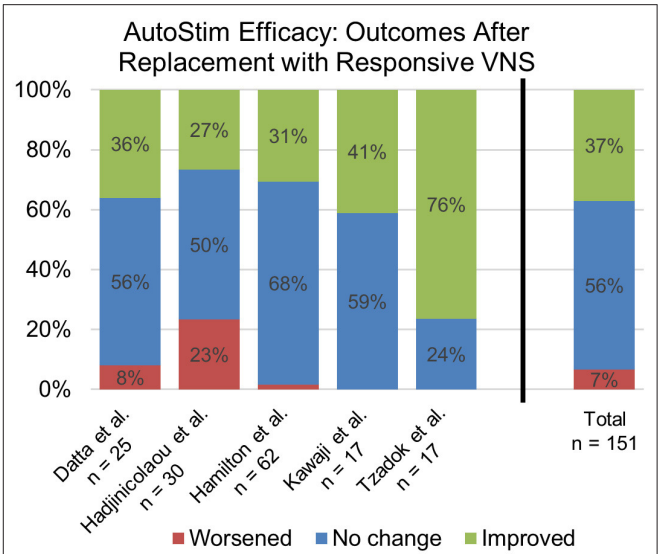

FIGURE 1 | Summary of data reported on patients with traditional VNS after replacement with a modern VNS generator with AutoStim enabled (20–24). The bar graph on the far right represents collated data from all five studies.

DOSING VNS THERAPY®

Vagus nerve stimulation is an electroceutical, and dosing is similar to that of a pharmaceutical. Instead of dosing in milligrams, VNS is dosed in milliamps (mA) of electrical current, and it is often true that higher output currents increase the likelihood that vagus nerve fibers will be activated (25, 26). Similar to a medication, the output current of VNS needs to be titrated up to achieve a therapeutic effect. Titration typically begins 2 weeks after implantation giving the patient some time to heal from surgery. The goal of titration is to optimize output current to a therapeutic level that is well-tolerated by the patient. Suggested programming involves starting at a normal mode output current of 0.25 mA and increasing output current by 0.25 mA every 2 weeks to a maximal tolerated current, typically with a goal of 1.5–2.25 mA. This is often considered the "therapeutic dose." The speed of titration can vary and depends on the comfort level of the healthcare provider, patient, and caregiver. Patient tolerability relates to the degree at which the patient feels sensations or experiences side effects associated with VNS. The most common stimulation associated side effects are hoarseness and voice alterations (7, 27). Paresthesia, cough, and shortness of breath are the next most common side effects. Other less common side effects include dyspepsia (indigestion), vomiting, increased incidence of obstructive sleep apnea, and hiccups. It is important that increases in output current are conducted at a rate that is tolerable and comfortable to the patient, however, patients are known to have better outcomes when they achieve a dose of 1.5–2.25 mA (26, 28). Over time, patients better tolerate VNS and the side effect profile diminishes (7, 27).

Once activated, VNS delivers a train of pulses with the pulse amplitude being the output current. Other programmed parameters include the pulse width (μs) and signal frequency (Hz) which represents the number of pulses per second. The level of vagus nerve activation is dependent on the combination of these three parameters which exhibit a conventional strength-duration relationship (29). Therefore, shorter pulse widths may require higher output currents to achieve a similar response. Default settings for pulse width and signal frequency are 250 μs

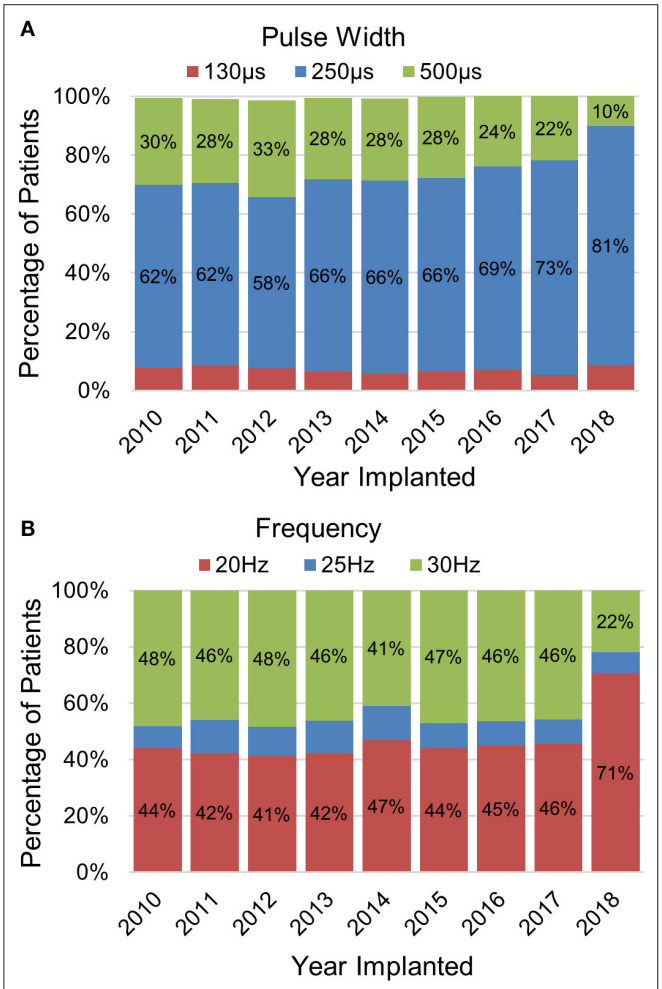

FIGURE 2 | Trends in programming VNS **(A)** frequency and **(B)** pulse width settings. The data represent programming data collected at least 12 months after being implanted with VNS (data on file at LivaNova).

and 20 Hz for the model 1000 SenTiva® generator while previous generators defaulted to 500 μs and 30 Hz. The use of lower pulse width and frequency settings of 250 μs and 20 Hz have been reported to result in similar efficacy with improved battery life as compared to higher settings of 500 μs and 30 Hz (26, 28). Lower pulse width and frequency settings are also often programmed to manage stimulation associated side effects (28). Experience with programming VNS, combined with these changes in default settings, have led to a shift in programmed pulse width and frequency settings. For patients implanted with VNS in 2018 with 12 or more months follow-up, ∼70% were programmed to 20 Hz and ∼80% were programmed to 250 μs (**Figure 2**). Prior to 2018, the percentage of patients programmed to 20 or 30 Hz were split fairly evenly. Since 2010, the usage of a 250 μs has increased from ∼60 to 80%.

Vagus nerve stimulation therapy delivers stimulation at set intervals throughout the day and night. The total percentage of time VNS Therapy® is on for an individual patient is called the duty cycle. Patients typically begin with a normal mode stimulation on time of 30 s and off time of 5 min, equating to a 10% duty cycle. While some patients can achieve benefits at a 10% duty cycle, others will experience additional benefit from increasing the duty cycle, typically by shortening the VNS off time. An example would be to maintain the normal mode stimulation on time of 30 s and decrease the off time to 3 min, equating to a 16% duty cycle. Further increasing the duty cycle and reducing the off time to ≤ 1.1 min, has shown to provide additional benefit to those still having seizures at lower duty cycles (30, 31). Shorter off times are associated with a lower number of AutoStims (19), and for off times <1 min, Autostim cannot be enabled.

Magnet mode output current is typically set 0.25 mA higher than normal mode. When VNS is initially activated, the normal mode output current is 0.25 mA and the magnet mode output current is set to 0.5 mA. As the output current is increased by 0.25 mA, the magnet current is also increased by 0.25 mA. The patient can often feel the magnet mode stimulation at this higher setting and may have minimal but tolerable side effects such as voice changes. Tolerability of the higher magnet mode setting can also be an indication the patient has acclimated to the next step up in dosage. For example, during the titration period, the patient can be asked to swipe the magnet multiple times to prepare for the next increase in output current. The magnet mode is typically programmed with a pulse width of 250 or 500 us and the on time is typically 60 s, although some patients may be set to 30 s or less. Magnet mode stimulation trumps all VNS modes and will deliver stimulation whenever the device is activated using the magnet.

AutoStim works in conjunction with normal and magnet modes. AutoStim output current is typically set 0.125 mA higher than that of normal mode, unless normal mode output current is 2 mA or higher, in which case the AutoStim current should equal the normal mode output current. The AutoStim pulse width is typically set to the same as that of normal mode, most commonly 250 μs, and the on time is typically 60 s, although some patients are set to 30 s. The sensitivity of the heart rate measurement is set in the operating room between 1 and 5, with 1 being the least sensitive. This should be verified prior to activation by comparing the patient's heart rate to the heart rate detected by the generator. An additional setting to be programed is the threshold for AutoStim. This typically starts at 40%, although added benefits may be seen in patients be decreasing the threshold to 30 or 20%. Once the heart rate increases by at least the percentage set as threshold, an AutoStim is delivered. This is followed by the normal mode off time, which can be no less than the AutoStim on time duration. Immediately following an AutoStim, there is an enforced off time equal to the AutoStim on time where an AutoStim cannot be triggered in order to avoid over stimulation of the nerve.

ADVANCED FEATURES

The model 1000 SenTiva® generator has advanced features available to simplify dosing, individualize therapy, and collect data (**Figure 3**). To aid in simplifying and standardizing dosing, Guided Mode is available which allows the programmer to adjust

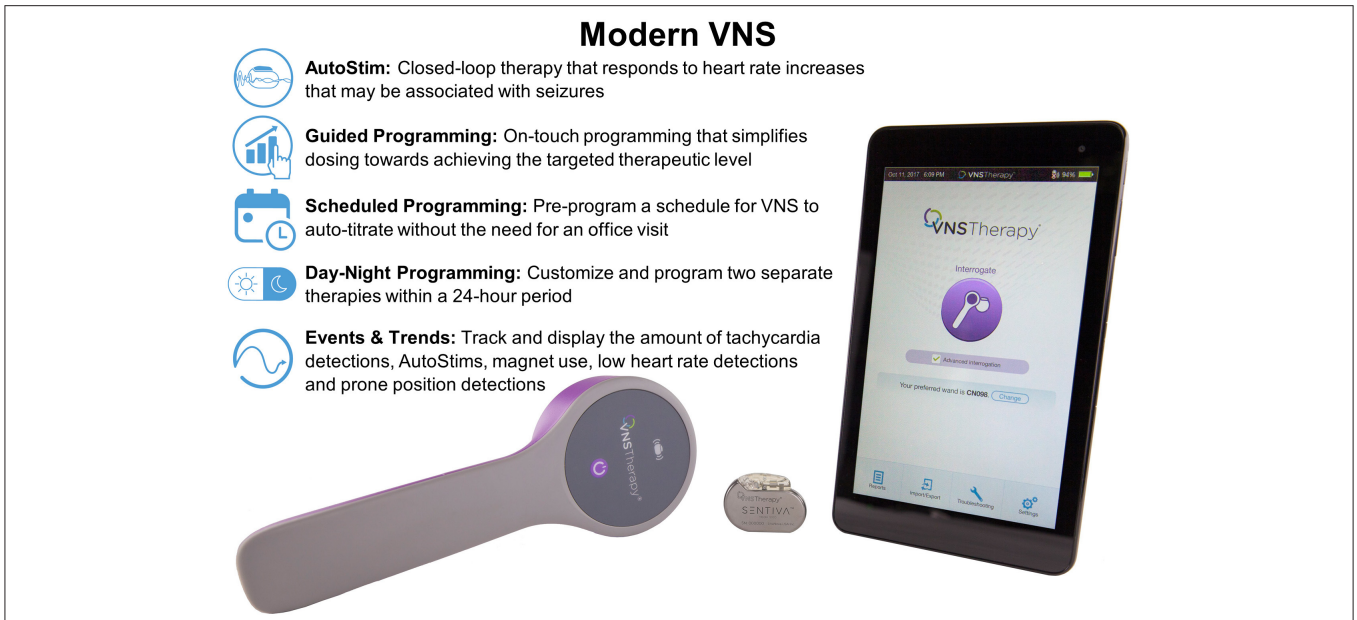

FIGURE 3 | Modern VNS allows additional features to traditional VNS including closed-loop AutoStim, Guided Programming, Scheduled Programming, Day-Night Programming, and Events and Trends data.

TABLE 1 | Standard protocol dosing steps.

Step	Output current (mA)		
	Normal	AutoStim	Magnet
1	0.25	0.375	0.50
2	0.5	0.625	0.75
3	0.75	0.875	1.00
4	1.00	1.125	1.25
5	1.25	1.375	1.50
6	1.50	1.62	1.75
7	1.75	1.875	2.00
Frequency:	20 Hz for all modes		
Pulse width:	250 μs for normal and AutoStim 500 μs for magnet mode		
Duty cycle:	10% (30-s on, 5-min off)		

settings with a single button. The steps in output current follow an FDA approved protocol based on published guidelines (28) known as the Standard Protocol (**Table 1**). A Custom Protocol can be created to adjust pulse width and frequency for each stimulation mode, adjust the normal mode duty cycle, or adjust the output current step size to 0.125 mA. The step size in output current cannot exceed 0.25 mA. Another added benefit of using the Standard or Custom Protocol is the ability to use Scheduled Programming which enables titration without required office visits. With Scheduled Programming, the healthcare provider can schedule the device to auto-titrate up to multiple steps on set days and times. The interval between steps is limited to 0.125 mA every 7 days or 0.25 mA every 2 weeks. This is especially useful for patients who have difficulty making office visits due to distance, limited mobility, or pandemic-related access or travel limitations. If telemedicine visits are an option, these can be set up on the same day or day after the auto-titration to assess tolerability and side effects remotely. It is important for the patient to have the magnet accessible when undergoing scheduled programming in case the patient experiences discomfort with increased levels of stimulation and therapy needs to be turned off.

The Day/Night Programming feature enables the delivery of different VNS parameters for two different time periods within a 24-h cycle. This feature is not available in Guided Mode and the programmer must be in Manual Mode. This feature is useful to mitigate side effects or provide a higher dose of VNS during certain times of the day or night. For example, if a patient has well-controlled daytime seizures but continues to predominantly have seizures at night, this feature may be used to deliver higher current at nighttime. For patients with obstructive sleep apnea, this feature may be beneficial in scheduling reduced pulse width, frequency and/or current at nighttime. For patients receiving AutoStim who exercise on a regular basis, Day/Night Programming can be used to turn off AutoStim or increase the AutoStim threshold during a specific timeframe to minimize or eliminate AutoStim associated with exercise induced heart rate increases. It is important to note that this setting does not adjust for daylight savings time or changes in time zones.

The programmer has an Events tab to view Events (summary data from recent office visits; **Figure 4A**) and Trends (daily and hourly trends of data; **Figure 4B**). Events displays a pie chart showing the daily distribution of normal mode, magnet mode, AutoStim, and Off time, as well as daily average number of stimulations for each mode. Overall duty cycle can

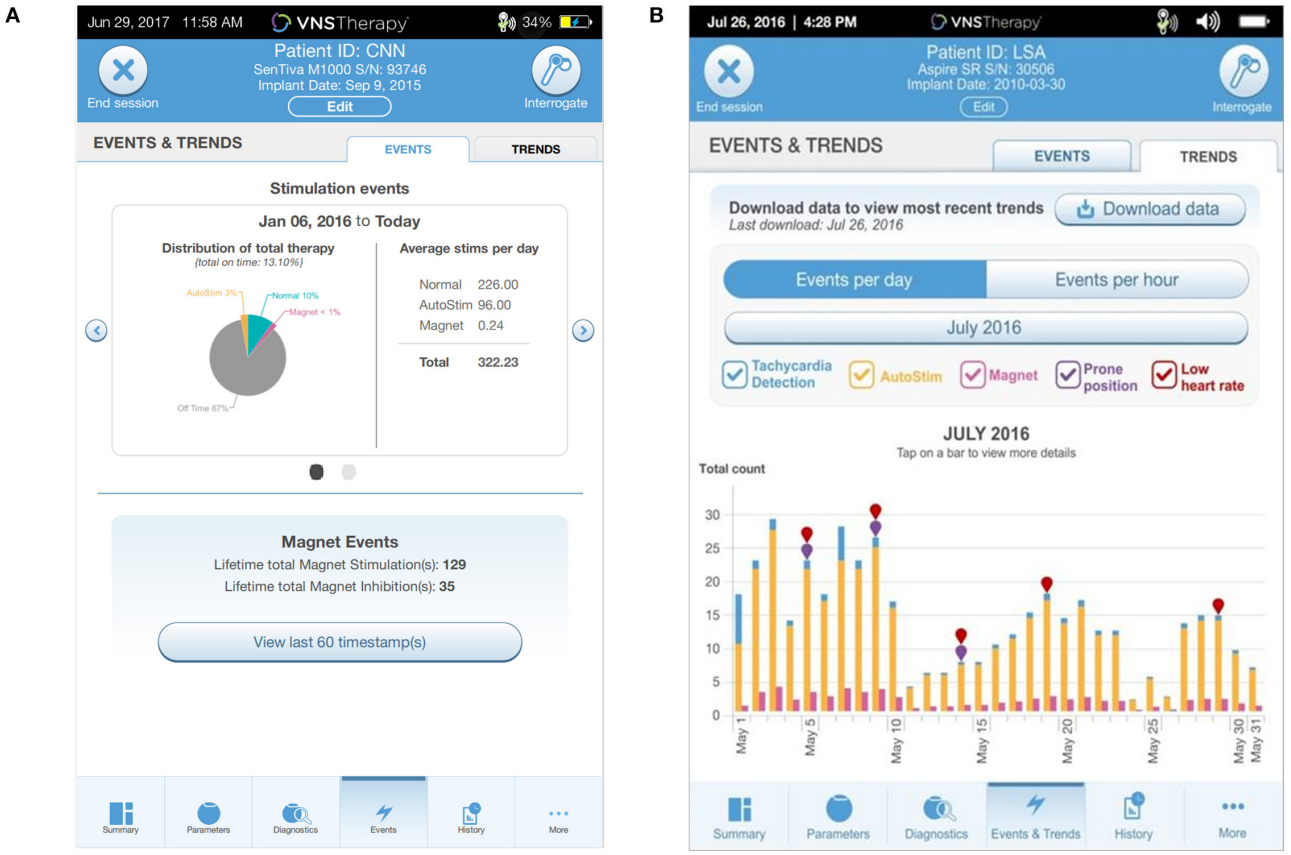

FIGURE 4 | The **(A)** Events tab displays a pie chart showing the distribution of daily Normal, AutoStim, and Magnet stimulations as well as average number of stimulations per day. The **(B)** Trends tab displays daily event counts for tachycardia detections, AutoStims, Magnet mode stimulations, prone position detections, and low heart rate detections.

also be viewed, combining total amount of time the normal, magnet and AutoStim features are active in a patient. Trends displays the daily or hourly number of tachycardia detections, AutoStims, and magnet mode stimulations. This can help guide future programming and patient education. For example, if the patient or caregiver report magnet activations that are not seen upon interrogation, additional counseling regarding the proper technique to activate the device should be reviewed. If the average AutoStims per day is low, you may want to lower the Autostim threshold to determine if lower thresholds lead to an increase in the average number of AutoStims and an associated decrease in either seizure frequency or duration.

The device can also be set to detect and track low heart rate and prone positioning which can be setup in the tachycardia detection window. The low heart rate threshold can be set to 30, 40, 50, or 60 beats per minute. Turning on prone position detection requires a simple calibration of the accelerometer within the generator. The generator will only sense for a low heart rate detection and prone positioning 7.5 min following an AutoStim or Magnet mode stimulation. A timestamp for these events can then be seen in the events and trends window. Prone position detection can only be used when tachycardia detection is enabled. This feature is currently only used for reporting purposes with no real-time notification or alarm in place when these events are detected. The results can be used to enhance your discussion of Sudden Unexplained Death in Epilepsy (SUDEP) with your patients and caregivers.

Magnetic resonance imaging (MRI) compatibility has expanded with the latest VNS devices, increasing access to high quality MRI scans. Patients implanted with functional single-pin leads and generator models 103 Demipulse®, 105 AspireHC®, 106 AspireSR®, or 1000 SenTiva® implanted in the typical upper chest location at or above the armpit area (above rib 4) can safely receive scans using a transmit body coil as long as its iso-center is outside C7-L3 (Group A in **Figure 5**). There are no restrictions on the type of receive coil that can be used. Use of a transmit body coil enables use of high channel count receive-only head coils which can be used to collect high quality MRI or functional MRI brain scans. Older generators, dual-pin generators, broken leads, or atypical generator implant locations are not compatible with transmit body coils and require use of extremity transmit/receive coils with the iso-center outside C7-T8 (Group B in **Figure 5**).

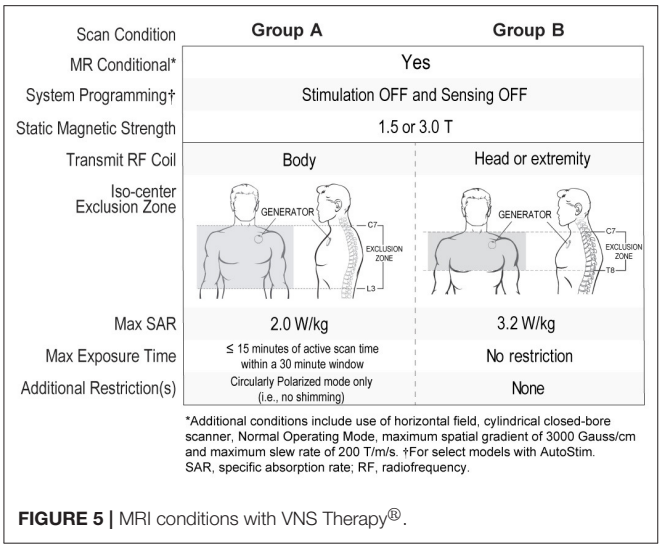

FIGURE 5 | MRI conditions with VNS Therapy®.

PRACTICAL MANAGEMENT OF VNS CLINICS

Development of a dedicated VNS clinic by an APP can lead to improved patient selection, patient education, and development of expertise by a core group of clinicians. Patients who are considered for VNS Therapy® are often presented at a multidisciplinary surgical case conference that includes neurology, neurosurgery, neuroradiology, neuropsychology, psychology, and other experts. Once the team determines the patient is a candidate for VNS, the patient should be scheduled to see the APP in a VNS clinic for a pre-VNS evaluation to discuss risks, benefits, side effects, dosing, and frequency of visits. It is important for the patient and family to understand the importance of follow-up and dosing after implantation because results depend on proper dosing to a therapeutic level (26, 28). The side effect profile of VNS Therapy® is unique in that it is does not cause central nervous system side effects seen with many anti-seizure medications (27). Treatment options that do not cause sedation or cognitive side effects are important to patients. While VNS is an adjunctive treatment along with anti-seizure medications, it is possible at times to reduce polypharmacy when VNS Therapy® is effective. Although few patients are rendered seizure-free with VNS Therapy®, the potential for reduction in seizure frequency, seizure duration, seizure clusters as well as the potential for other improvements in quality of life should be reviewed. Discussion of surgical risks should include risk of infection as well as the rare complication of vocal cord paralysis. Magnetic resonance imaging restrictions should be reviewed and a thorough review of the patient's medical history will help with direct counseling on potential contraindications associated with MRI. Patients with a history of reflux, apnea, arrythmia or bradycardia need to understand the potential for worsening symptoms. Evaluation by a cardiologist is recommended for patients with predisposed dysfunction of cardiac conduction systems.

Patients should be made aware that the generator will need to be replaced periodically as the battery life is typically between 5 and 10 years and depends on the level of VNS settings. More frequent follow-up, such as every 3 months, may be required after the VNS generator has been in place for several years in order to monitor battery life. The lead will be left in place unless there is a serious reason for removal. Removal of the lead and electrode can be done, however there is a risk of damaging the vagus nerve, and generally should not be undertaken unless the benefit of removal clearly outweighs the risk of the procedure. Coordinating a pre-VNS counseling session with an evaluation by neurosurgery allows for a strong handoff to the surgeon with VNS relevant information provided by the APP. It also provides a more comprehensive approach to ensure the patient and guardians have adequate information to make an informed decision about proceeding with VNS placement. Once a patient or guardian elects to move forward with VNS placement, informed consent is obtained, surgery is scheduled, and a follow up visit in the VNS clinic should be scheduled for 2 weeks after implantation. The patient is typically given a magnet kit upon implantation that should be brought to each follow up visit.

At the VNS activation visit, the APP begins by assessing the incisions to ensure they are healing without signs of infection. At the time of activation, patients will often experience a voice change characterized by a deepened tone or a warble to their voice during VNS on time, or the patient may cough at the onset of stimulation. Patients who experience throat clearing or a mild cough often find that the symptoms subside within 1 to 2 days, however this can be a dose limiting side effect in the beginning of therapy. Over time patients tend to better tolerate VNS settings as side effects resolve and further dose titration is possible. Voice changes can also improve with time, but can become more pronounced with subsequent increases in current. Although this is a common side effect, it typically does not limit the ability to titrate therapy. With each dose titration, the APP should monitor for signs of discomfort, coughing, or other intolerable side effects, and be prepared to decrease the dosing parameters if needed. For newly implanted patients, the APP can increase the dose in a stepwise fashion such as that in **Table 1** and monitor the patient for side effects during the visit. It is often possible to increase the output current multiple steps during the first visit. If side effects of cough or voice change occur while slowly titrating the dose over a 30 min period, then the APP can step back to the last previously tolerated output current.

Once activated, patients and caregivers should be instructed in the proper use of the magnet. Discussion around the times to use the magnet, frequency of magnet activation for a single event, and the proper technique to turn off the device with the magnet should be reviewed. Those present at the visit should also demonstrate the proper technique to use the magnet. It can be helpful to review magnet activations recorded by the device to see if the patient and family are correctly using the magnet at home. It is also helpful to provide a letter for all caregivers to explain the use of the magnet, as well as magnet restrictions.

Monitoring battery life throughout follow-up is important in order to properly plan for a generator replacement procedure prior to battery depletion. As the battery becomes low, device

diagnostics will show the following battery life indicators: Intensified Follow-up Indicator (IFI), Near End of Service (NEOS) and End of Service (EOS) when the battery life is 8–18%, 0–8%, and 0%, respectively. When the battery life indicator is displaying IFI, it is recommended to schedule more frequent follow-up visits with the patient, such as every 3 months, in order to closely monitor battery life. The full benefits from VNS may take years to fully appreciate (7), and benefits may be lost acutely or gradually, and possibly permanently after EOS (32). It is therefore important to weigh all potential benefits of VNS in addition to seizure control when considering generator replacement, including effects on alertness, post-ictal state, cluster seizures, mood, and memory. Generator replacement should be done prior to EOS to ensure long-term treatment. Patients should also be informed that if they experience a sudden change in seizure frequency, decreased perception of stimulation, or loss of other VNS-induced effects after being implanted for several years, the device should be checked to see if the battery is near end of service. For patients with older generation dual-pin leads, a dual-pin compatible generator is required for replacement, such as the model 104 generator. If a dual-pin compatible generator is not available in a specific region, then a lead replacement would be required during the generator replacement procedure. If discontinuation of therapy is being considered due to lack of efficacy or intolerable side effects, VNS Therapy® can be turned off for an extended period of time, such as 6 months, to determine if seizure activity or other potential VNS-induced benefits change. If it is determined that VNS was not beneficial to the patient, the device may remain implanted but with all output current settings programmed to zero, or for patients who prefer, the VNS system can be fully or partially explanted (33, 34).

TROUBLESHOOTING

The benefit of a trained APP is the knowledge to troubleshoot and ability to see patients for urgent visits should problems arise. Difficulties with interrogation can occur. If this arises the battery power of the wand should be assessed and batteries should be replaced if needed. If the battery light on the wand is green, reposition the wand to attempt interrogation. If the Bluetooth connection between the wand and tablet are not adequate, connect the wand to the tablet via the cord provided with the device. In some cases, repositioning of the patient's arm or placing the patient supine is needed to make the device more accessible to the wand.

When interrogating the device, a high or low lead impendence may be detected. This can occur with lead discontinuity, disconnection or fibrosis. If a high impedance error message comes up soon after surgery this could be due to the setscrew or lead pin not being fully inserted into the generator. If a high lead impedance message occurs in an established patient, this could indicate a lead break and all output currents should be turned off. Obtaining an x-ray to visualize the lead is often indicated if there is a high or low lead impedance, however it is possible for the break in the lead to be small and not visible on x-ray.

Other than technical difficulties, an appropriate understanding of managing side effects is imperative for any provider running a VNS clinic. Many dose related side effects, such as reflux, cough, voice change and sleep apnea can be addressed by adjusting the settings. This includes decreasing the output current, signal frequency, pulse width or duty cycle. For patients who are unable to tolerate a higher output current, the duty cycle can be increased and may provide additional benefit. Some patients are bothered by the noticeable difference in normal mode and AutoStim output current. In these cases, AutoStim can be set at the same output current as normal mode. Taping the magnet in place to temporarily turn off VNS Therapy® can be done during eating for patients who note difficulty in swallowing or can be done during singing or public speaking in patients who experience stimulation induced voice alterations. In these situations, the magnet should be removed immediately after eating, singing, or public speaking is complete. It is important to know that no stimulation will occur if the magnet is taped or continually held in place over the VNS. This technique of placing the magnet over the generator can also be used if there is concern the VNS is not tolerated as evidenced by painful stimulation, intense neck pain, or trouble breathing. The magnet can be taped in place until the patient is able to obtain medical attention.

In rare cases, patients have reported discomfort along the track of the lead, but interrogation failed to reveal any abnormality. Intraoperative examination has revealed degradation of the casing around the wire, which caused the patient pain without triggering an abnormal diagnostic. If a patient consistently reports a problem, the provider must consider that there may be something wrong that is not detectable by standard interrogation, and refer the patient back to the surgeon.

Vagus nerve stimulation is an efficacious intervention for DRE, but it will not benefit every patient. There may be times when patients do not feel they have benefitted from the device, and they wish to have it removed. Every center will establish its own criteria for explanting a VNS, but it is reasonable to wait until the patient has had it on reasonably optimized settings for 2 years, and every effort should be made during that time to ensure the best settings the patient can tolerate are achieved. If the patient and care team think VNS removal is warranted due to lack of efficacy, they may wish to consider simply turning off the device for 6 months before explanting it. This gives the patient a chance to see if perhaps the VNS was providing more benefit that previously realized. Tracking cognitive abilities, mood, and quality of life scores during this time would be helpful in determining if the patient notices any deterioration in these metrics without the VNS on.

CONCLUSION

Vagus nerve stimulation is a well-established adjunctive treatment in reducing seizure frequency in patients with DRE, and VNS has evolved into a smarter technology over the past decade with the addition of closed-loop stimulation and

features the enable guided and scheduled dosing and more individualized therapy. Advanced Practice Providers play a critical role in dedicated VNS clinics which provide value to patients and caregivers through improved access, education, and continuity of care. Continued education on the practical use of traditional and modern VNS features as described in this review is important to maximize benefit to VNS patients.

AUTHOR CONTRIBUTIONS

All authors contributed to the first five sections describing VNS Therapy®. The sections PRACTICAL MANAGEMENT OF VNS CLINICS and TROUBLESHOOTING were written exclusively by the advanced practice provider authors BF, JD, EK, and SM.

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Transcutaneous auricular vagus nerve stimulation induces stabilizing modifications in large-scale functional brain networks: towards understanding the effects of taVNS in subjects with epilepsy

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Transcutaneous auricular vagus nerve stimulation (taVNS) is a novel non-invasive brain stimulation technique considered as a potential supplementary treatment option for subjects with refractory epilepsy. Its exact mechanism of action is not yet fully understood. We developed an examination schedule to probe for immediate taVNS-induced modifications of large-scale epileptic brain networks and accompanying changes of cognition and behaviour. In this prospective trial, we applied short-term (1 h) taVNS to 14 subjects with epilepsy during a continuous 3-h EEG recording which was embedded in two standardized neuropsychological assessments. From these EEG, we derived evolving epileptic brain networks and tracked important topological, robustness, and stability properties of networks over time. In the majority of investigated subjects, taVNS induced measurable and persisting modifications in network properties that point to a more resilient epileptic brain network without negatively impacting cognition, behaviour, or mood. The stimulation was well tolerated and the usability of the device was rated good. Short-term taVNS has a topology-modifying, robustness- and stability-enhancing immediate effect on large-scale epileptic brain networks. It has no detrimental effects on cognition and behaviour. Translation into clinical practice requires further studies to detail knowledge about the exact mechanisms by which taVNS prevents or inhibits seizures.

Epilepsy is one of the most common neurological disorders and is defined by recurrent epileptic seizures. Although two thirds of affected subjects achieve seizure-freedom with the first two appropriately chosen antiseizure medications (ASM)[1], the other third requires extensive therapy attempts in order to achieve seizure-freedom or at least an acceptable seizure situation. Even the development of new ASM has not led to a significant improvement of seizure outcome, though tolerability and interaction profile have become more advantageous[2]. Thus, there is a strong need for alternative or complementary treatment options. Vagus nerve stimulation (VNS) is an established method of brain stimulation in several diseases, including epilepsy[3]. Invasive vagus nerve stimulation (iVNS) was first approved as early as in the 1990s. It has been extensively studied and its safety has been demonstrated in more than 20 studies. Its effectiveness is assumed with a responder rate (subjects in whom seizure frequency is reduced by more than 50%) of approximately 50%[4,5]. However, it is an invasive method with need of anaesthesia and surgical risk. Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive external stimulation (of the auricular branch of the vagus nerve) and seems to be an interesting alternative. Good

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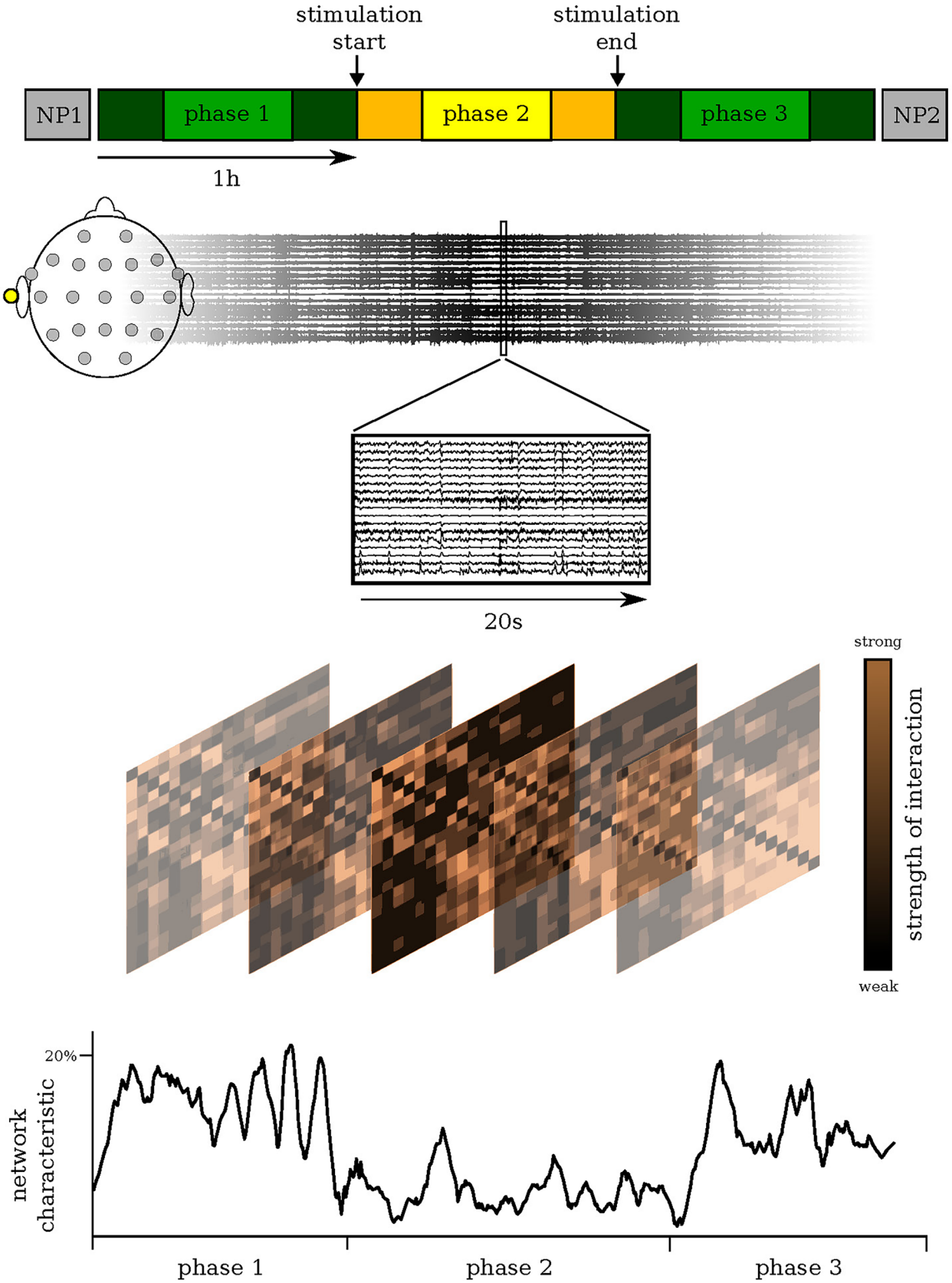
stimulation start
stimulation end
NP1
phase 1
phase 2
phase 3
NP2
1h
20s
strong
strength of interaction
weak
20%
network characteristic
phase 1
phase 2
phase 3

◂**Figure 1.** Examination schedule: Probing for taVNS-induced changes in epileptic brain networks. Our examination schedule consisted of a 3-h EEG recording (Methods) that covered a stimulation phase (phase 2; continuous stimulation of the left cymba conchae) and a pre- and post-stimulation phase (phase 1 and phase 3, resp.). In our analyses, we neglected data from the first and last 15 min of each phase (darker colours) in order to remove possible transient effects. The EEG recording was preceded and followed by a standardized neuropsychological assessment (NP1 and NP2, resp. 30 min; Methods). We derived evolving epileptic brain networks from the EEG recording using a sliding-window approach (Methods), assessed important global characteristics of each network (Methods), and tracked their changes over time.

tolerability and effectiveness have been demonstrated for taVNS[6–10]. For both iVNS and taVNS, similar projections of afferent vagus nerve fibres to the nucleus of the solitary tract could be shown[11] and cerebral activation patterns induced by iVNS and taVNS resemble each other (for overview see[12]).

Knowledge about immediate and longer-lasting VNS-related changes of brain activity is sparse. In contrast to other, locally specific stimulation methods such as deep brain stimulation (DBS)[13] or responsive neurostimulation (RNS)[14], it is generally assumed that VNS leads to a rather unspecific, global activation of various brain structures (including thalamus, limbic system, insular cortex)[15,16]. This local unspecificity is also reflected in contradicting findings on the EEG: while some authors report a modification of epileptiform activity[17], quantitative EEG studies point to opposing phenomena (e.g., synchronisation vs. desynchronisation[16]) as well as to ambiguous changes in relevant EEG frequency bands[18].

We hypothesized that the impact of the global, apparently unspecific activation can be suitably assessed with a global analysis approach which makes use of the EEG derived so-called evolving functional brain networks[19,20]. The powerful mathematical framework of network theory provides means to determine important network characteristics such as their topological, stability, and robustness properties. Tracking network characteristics over time would allow one to identify and delineate stimulation-related changes of EEG activity. Accompanying such an investigation with an examination of cognitive functions may provide important insights into their possible relationships with the aforementioned network characteristics[21] and could help to improve understanding of whether and how VNS may impact cognition[22,23]. We tested this hypothesis by investigating whether short-term taVNS induces measurable immediate modifications of functional brain network in subjects with epilepsy and whether modifications are accompanied by changes of cognition and behaviour (see Fig. 1).

Results

Stimulation-related modifications of evolving epileptic brain networks. Evolving epileptic brain networks are functional networks[19] that can be derived from EEG recordings by associating network vertices with brain regions sampled by electrode contacts and network edges with the time-varying estimates of the strength of interactions between pairs of brain regions[20] (Methods). We derived such evolving, fully connected and weighted networks from a time-resolved synchronisation analysis of the 3-h EEG recording, used various measures (Methods) to assess important characteristics of each network and tracked their changes over time. In order to characterise the network's global topological properties, we estimated its average shortest path length L and its average clustering coefficient C. In addition, we assessed the network's stability and robustness properties by estimating its synchronisability S and its assortativity A. The average shortest path length characterises the network's functional integration; the lower L, the more integrated is the network. The average clustering coefficient characterises the network's functional segregation; the lower C, the more segregated is the network. Synchronisability assesses the network's propensity (or vulnerability) to get synchronised by an admissible input activation: the lower S, the more easily can the synchronised state be perturbed. Assortativity assesses the tendency of edges to connect vertices with similar or equal properties. If edges preferentially connect vertices of similar (dissimilar) property, such networks are called assortative (disassortative). Disassortative networks are more vulnerable to perturbations and appear to be easier to synchronise than assortative networks. The latter show a stronger tendency to disintegrate into different groups than disassortative networks.

In the majority of subjects (Fig. 2), taVNS led to immediate, stimulation-related alterations in the overall strength of functional interactions (global synchronisation level R) in epileptic brain networks. Their average shortest path length L, average clustering coefficient C, synchronisability S, and assortativity A were seen to be modified in a similar number of subjects. Interestingly, taVNS appeared to have a persistent effect in about 30–50% of subjects, as seen with most network characteristics (for those subjects, for which we achieved significant differences between phases ($p < 0.05$ after Bonferroni correction, Mann–Whitney U values ranged between 173 and 3187 (phase 1 $\rightarrow$ 2), between 23 and 3231 (phase 2 $\rightarrow$ 3) and between 585 and 3301 (phase 1 $\rightarrow$ 3); ranges are reported for all network characteristics; the number of degrees amounted to 90 for each phase).

We provide a more detailed picture of stimulation-related alterations of network characteristics in Fig. 3, where we plot the distributions of their relative changes for networks transiting between the different phases. The global synchronisation level R slightly decreased from the pre-stimulation to the stimulation phase (desynchronisation; phase 1 $\rightarrow$ 2: −5%; we report the median values in the following) but it increased when networks transit from the stimulation to the post-stimulation phase (re-synchronisation; phase 2 $\rightarrow$ 3: 10%). We observed only slight differences between the pre- and post-stimulation phase (phase 1 $\rightarrow$ 3: 4%). Together with the high interindividual variability, these findings partly confirm previous observations with long-term iVNS[24,25] or immediate iVNS[26].

For the average shortest path length L, we attained a similar though inverted patterning (which is to be expected given the definition of a path length in a weighted network): a slight increase of L from the pre-stimulation to the stimulation phase (phase 1 $\rightarrow$ 2: 6%), a slight decrease from the stimulation to the post-stimulation

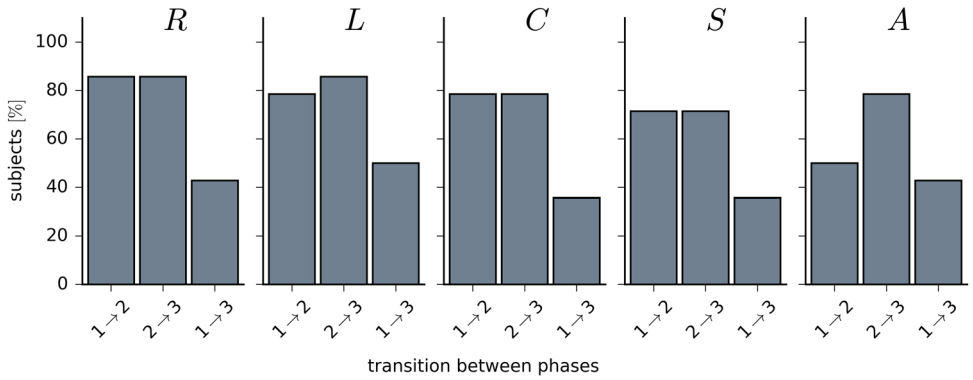

Figure 2. Percentage of subjects for which taVNS led to significant differences (Methods) between networks characteristics from phases 1, 2, and 3; global synchronization level R, average shortest path length L, average clustering coefficient C, synchronisability S, and assortativity A.

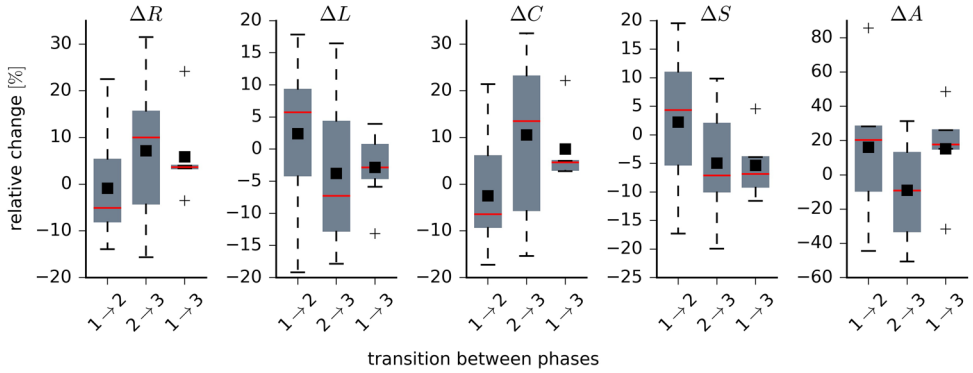

Figure 3. Distributions of taVNS-related alterations in network characteristics. Boxplots of relative changes Δ in network characteristics. Relative changes calculated as $\Delta = (M_l - M_k)/M_k$, where M_k and M_l denote placeholders for the temporal means of the respective characteristics from phase k and phase l (global synchronization level R, average shortest path length L, average clustering coefficient C, synchronisability S, and assortativity A). During phase 1, network characteristics attained the following values: $R = 0.31 \pm 0.02$, $L = 3.43 \pm 0.29, C = 3.33 \pm 0.02, S = 3.15 \pm 0.49$, and $A = 0.37 \pm 0.15$. Bottom and top of a box are the first and third quartiles, and the red band and the black square are the median and the mean of the distribution. The ends of the whiskers represent the interquartile range of the data. Outliers are marked by a + sign.

phase (phase 2 → 3: −7%), and slight undershoot effect when comparing the pre- and post-stimulation phase (phase 1 → 3: −3%).

We can derive similar indications with changes of the average clustering coefficient C, for which we observed a patterning that compares to the one seen for the global synchronisation level, although changes were slightly more pronounced (phase 1 → 2: −6%; phase 2 → 3: 14%; phase 1 → 3: 5%).

Synchronisability S slightly increased from the pre-stimulation to the stimulation phase (phase 1 → 2: 4%) and it decreased when networks transit from the stimulation back to the post-stimulation phase (phase 2 → 3: −7%). A similar decrease was observed when comparing the pre- and post-stimulation phase (phase 1 → 3: −7%).

Interestingly, we obtained strongest indications for a preventive effect of taVNS with changes in the networks' assortativity A. Already during the pre-stimulation phase, epileptic brain networks were seen to be assortative ($A = 0.37 \pm 0.15$). taVNS even increased their assortativity (phase 1 → 2: 20%). Although networks experienced a slight decrease of their robustness when transiting from the stimulation back to the post-stimulation phase (phase 2 → 3: −7%), the comparably strong increase seen between the pre- and post-stimulation phase (phase 1 → 3: 18%) would point to an enduring robustness-enhancing effect of taVNS.

Stimulation-related modifications of cognition and behaviour. Prior to stimulation, 35% of subjects presented with impaired executive functions. Mild or severe impairment in verbal memory was seen in 82%, and a relevant depressive symptomatology in 43% of subjects. After stimulation, we observed in two subjects a significant intraindividual improvement of executive functions. All other cognition-related variables remained unaffected in these and the other subjects (Mann Whitney U values ranged between 64 and 98 for the different domains; the number of degrees of freedom amounted to 14; n.s.). No significant self-perceived changes in the

evaluated domains cognition, behaviour and physiological symptoms were observed; one subject reported an improvement in anxiety after taVNS. There were no significant relationships between neuropsychological variables and characteristics of epileptic brain networks.

Evaluation of the device: side effects and usability. No local side effects were complained or detected by clinical check-up. All subjects rated the handling of the device as good or very good. 86% felt that the continuation of their activities was not affected by the stimulation. The majority rated the wearing comfort as good or very good (79%). However, some subjects stated that the device is rather poorly suited for long-term use during the day (43%) or repeated use within one day (29%).

Discussion

With our prospective trial, we investigated whether short-term transcutaneous auricular vagus nerve stimulation (taVNS) induces measurable immediate modifications of functional brain networks in fourteen subjects with epilepsy and whether modifications are accompanied by changes of cognition and behaviour. Our findings reveal that taVNS has stabilising effects on networks in the majority investigated subjects and these effects persist in up to 50% of subjects. In contrast, cognition and behaviour are not affected by the stimulation.

The stimulation-related alterations seen for network characteristics average shortest path length and clustering coefficient indicate that taVNS modifies the network's topological organisation, which is reflected in a more integrated and less segregated network. Similar findings could be achieved only recently also with long-term invasive vagus nerve stimulation[27]. In addition to modifications of network topology, short-term taVNS can enhance stability and robustness of epileptic brain networks. The alterations seen for synchronisability indicate an increase of the network's stability against perturbations, i.e., a more resilient brain network. Moreover, the observed similar decrease in synchronisability when comparing the pre- and post-stimulation phases would point to an enduring stabilising effect of taVNS. Interestingly, we obtained strongest indications for a preventive effect of taVNS with changes in the networks' assortativity. Already prior to stimulation, epileptic brain networks were seen to be assortative, which confirms previous observations[28,29], and taVNS even increased their assortativity. Although networks experienced a slight decrease of their robustness when transiting from the stimulation back to the post-stimulation phase, the comparably strong increase seen between the pre- and post-stimulation phase would point to an enduring robustness-enhancing effect of taVNS.

There were no detrimental effects of taVNS on cognition and behaviour in our subjects with epilepsy. Similar observations were made recently in healthy subjects[30], even when stimulating the brain during the memory consolidation phase. However, findings need to be taken with care, given that research into the impact of taVNS on cognition is still in its infancy[31,32]. Previous studies revealed that long-term iVNS can enhance recognition memory in subjects with epilepsy in comparison to sham stimulation and depending on stimulation intensity[33]. Detrimental effects, however, were reported for acute high-intensity iVNS on figural memory but not on verbal memory in subjects with epilepsy[22]. Future studies would need to further elucidate the influence of taVNS on cognition and behaviour.

Short-term taVNS was well tolerated by our subjects with epilepsy, and no local side effects occurred. These results are in par with expected results from long-term studies[34]. The usability of the device was rated good and very good in terms of handling, management, comfort, and possibility of continuation of one's activities. However, rating for suitability for long-term or repeated use was viewed critically by some subjects. Complaints about the duration of a daily stimulation of 4 h were given by subjects with epilepsy in treatment settings before and recently led to an evaluation of the effects of reduced stimulation times[9].

Brain stimulation is a rapidly evolving field and is considered as a supplementary treatment option for subjects with refractory epilepsy. Invasive VNS is accompanied with perioperative risks involved with device implantation and is thus limited to the treatment of more severe, drug-resistant cases. taVNS is a non-invasive brain stimulation technique and clinical data about efficacy and tolerability indicate this approach to be an interesting alternative. Nevertheless, we still lack detailed knowledge about the exact mechanisms—from the molecular[35] to the brain level and to other organs (e.g. heart[36])—by which taVNS prevents or inhibits seizures which currently hinders the translation into clinical practice[37]. Our findings point to a topology-modifying, robustness- and stability-enhancing immediate effect of short-term taVNS on large-scale epileptic brain networks. At least on the time scale considered in our study (few hours), these network modifications did not impact on the investigated variables of cognition and behaviour. Our approach thus opens new perspectives towards improving our understanding of the dynamics of large-scale epileptic brain networks as well as towards deciphering the mechanism of action of taVNS.

Future studies should investigate the impact of long-term transcutaneous auricular vagus nerve stimulation on brain networks as well as long-term effects of the stimulation to deepen understanding of the mechanism of action and the potential efficacy of taVNS. By the same token, future studies should also investigate the impact of stimulation on local and/or medium-scale properties of epileptic brain networks (such as centralities of vertices and edges, cores, motifs, or community structures) as this could help in optimizing stimulation parameters which are currently selected rather heuristically. Comparing the effects of iVNS and taVNS using the same study design could reveal similarities and differences of these stimulation approaches with regard to large-scale epileptic networks. And finally, evaluation of subjects with different epilepsy syndromes and different severities could help translating this brain stimulation approach into clinical use.

There are some limitations of our prospective investigations. Since we avoided as much confounders on the EEG-evaluation as possible (e.g. by activation methods, change of ASM, seizures before study), we generated a high exclusion rate that led to a small number and higher heterogenicity of investigated subjects with epilepsy. A larger group size as well as more homogeneous groups could be interesting. The device we used for taVNS

	Sex	Age	Dur.	Lat.	Loc.	Hand.	MRI lesion	Drug res.	ASM	Stim.
1	f	50	1	Right	Insula	Right	Yes	No	LEV	3.0
4	f	19	0	Left	Frontal	Right	No	No		0.9
5	m	18	0	Right	Temporal	Ambidexter	No	No	LEV	0.9
6	m	25	1	Unknown	Unknown	Right	No	No		3.5
7	f	22	7	Right	Frontal	Right	No	Yes	LCM	0.6
9	f	55	4	Right	Temporal	Right	No	Yes	LEV, TPM	3.0
11	f	24	12	Bilateral	Temporal	Right	No	Yes	BRV, LTG, LCM	3.0
12	f	70	60	Right	Temporal	Right	Yes	Yes	LTG, VPA, PB	0.9
14	m	71	1	Left	Temporal	Right	No	No	LEV	1.4
15	m	26	19	Left	Frontal	Right	Yes	Yes	LEV, LTG, VPA, OXC	1.9
17	f	25	5	Right	Frontal	Right	No	Yes	CBZ	2.9
18	m	77	2	Left	Temporal	Right	No	No	LEV	1.6
19	f	53	34	Left	Temporal	Right	No	Yes	LTG, ZON	1.9
20	m	40	17	Right	Temporal	Right	No	Yes	LEV, OXC	2.7

Table 1. Patient demographics. Dur.: duration of disease in years; lat. = lateralization; loc. = localisation; hand. = handedness; drug res. = drug resistance according to ILAE[40]; ASM = antiseizure medication; LEV = levetiracetam, LTG = lamotrigine; LCM = lacosamide; TPM = topiramate; BRV = brivaracetam; VPA =valproate; PB = phenobarbital, OXC = oxcarbazepine, CBZ = carbamazepine; ZON = zonisamide; stim. = stimulus intensity in mA.

has non-adjustable stimulation parameters. However, in iVNS, adjusting parameters individually is not only crucial for an effective treatment of epilepsy[38,39], but might also impact on topological and robustness properties of epileptic brain networks. Evaluating the impact of varying stimulation parameters could contribute to the understanding of the mechanism of actions of taVNS and, in the long run, help to optimize its clinical use.

To conclude, short-term taVNS has a topology-modifying, robustness- and stability-enhancing immediate effect on large-scale epileptic brain networks. It has no detrimental effects on cognition and behaviour and was well tolerated by our subjects with epilepsy. There are similarities between taVNS and iVNS that emphasise the necessity of further research on taVNS as the less complicated way of brain stimulation via the vagus nerve.

Methods

Subjects. Between March 25 and September 19 of 2020, 472 subjects were admitted to our ward and were screened for suitability for our study. Exclusion criteria were unclear diagnosis, progressive disease, previous resective brain surgery, actual or previous vagus nerve stimulation or deep brain stimulation, insufficient German language capability, mental disability and incompetence to follow instructions. Inclusion criteria were clinical necessity for long-term video EEG-recording and proven diagnosis of epilepsy. Of the 36 eligible subjects, 22 declined participation. Fourteen subjects signed informed consent after being provided with written information and being given the opportunity to ask further questions; these subjects were included in the study. The study protocol had been approved by the ethics committee of the University of Bonn before the study has started. All experiments were performed in accordance with relevant guidelines and regulations.

Fourteen subjects with epilepsy (8 females; age 18–77 years, median 41 years; Table 1) were included in the study. Eight subjects had a drug-resistant epilepsy according to the definition of the International League against Epilepsy[40]. We applied taVNS with individualized stimulation intensities (range: 0.6–3.5 mA. mean 2.0, SD ±1.0, Methods) for 1 h in the early afternoon while subjects underwent a continuous 3-h EEG recording (see Fig. 1). No activation methods (such as change in ASM, hyperventilation or sleep deprivation) were applied at least 24 h before stimulation. The EEG recording was preceded and followed by a standardized neuropsychological assessment which involved measures of executive functions, verbal memory, mood, and the rating of subjective changes of the subjects' cognitive, psychiatric and somatic condition. To reduce potential practice effects, parallel test versions were applied for examining executive functions and verbal memory. No side effects were reported or observed.

Transcutaneous auricular vagus nerve stimulation. Stimulation was carried out with two hemispheric titanium electrodes of a NEMOS device (tVNS Technologies GmbH, Erlangen, Germany) fitted in the left cymba conchae and using a common set of non-adjustable parameters (biphasic signal form, impulse duration 20 s, impulse pause 30 s, impulse frequency 25 Hz). Intensity of stimulation was adjusted individually and was raised slowly until the subject noticed a "tingling", but no pain.

Details of neuropsychological assessment. *Attention and executive functions*. The EpiTrack 3rd edition[41] is a screening tool consisting of six subtests assessing response inhibition, visuo-motor speed, mental flexibility, visuo-motor planning, verbal fluency, and verbal working memory. It can be completed in 15 min. The performance in each subtest results in an age-corrected total score with a maximum score of 49 points (after

age-correction). Mild impairment is reflected by a total score in the range of 29 to 31, the cut-off score for severe impairment is $\leq$ 28 points ($>$ 2 SD below the normative sample). A significant intraindividual change in the total scores between two assessments is indicated by a gain of $\geq$ 4 points or the loss of $\geq$ 3 points.

Verbal memory. Verbal memory was assessed using a short version of the Verbal Learning and Memory Test (VLMT[42]) which is the German adaptation of the Rey Auditory Verbal Learning Test (RAVLT). The shortened VLMT version includes two consecutive trials of word list learning (15 words) with immediate free recall. After the two learning trials, the EpiTrack was performed, followed by the delayed free recall of the word list. Thus, the EpiTrack provided a distraction for memory testing. Age-correction was based on normative data of 383 healthy subjects. Scores for learning, memory and loss over time were transformed into a scale ranging from 1 to 7 according to the normative sample and converted into a total memory score ranging from 3 to 21. After age correction, total memory scores from 14 to 18 are rated as normal, scores $>$ 18 as above average, scores from 11 to 13 as mild impairment, and scores of $\leq$ 10 are considered a significant impairment. A significant change is indicated by a gain of $>$ 3 points or a loss of $>$ 5 points.

Mood/Depression. The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E[43]) is a brief self-report questionnaire used as a screening tool for detecting depression in people with epilepsy. This 6-item screening instrument specifically focuses on symptoms of depression that cannot be explained by adverse effects of antiseizure medication. All items are rated on a four-tiered scale (1—never, 2—rarely, 3—sometimes, 4—always or often). A total score above 15 indicates a relevant depressive symptomatology.

Subjective measures. A modified version of the Adverse Events Profile was used before and after stimulation to assess self-perceived changes in three domains: (1) cognition (vigilance, energy, psychomotor speed, attention/ability to concentrate, fluent speech, verbal comprehension, word finding, remote memory), (2) behaviour (depression, anxiety, aggression, restlessness), (3) physiological symptoms (dizziness, drowsiness, nervousness, tremor, headache, nausea, dermatological symptoms, vision problems/double vision). Subjects were asked to rate the presence and severity of impairments on a four-tiered scale ranging from very good (0) to very bad (3). Total scores for each domain were calculated.

Questionnaire on the evaluation of the device. Seven ordinal questions were asked concerning handling, possibility to continue activities while using the device, feeling while using the device, comfort, suitability for long-term and repeated use.

EEG recordings and data pre-processing. We recorded electroencephalograms (EEG) from 19 electrode sites according to the 10–20 system and Cz served as physical reference. EEG data were sampled at 256 Hz using a 16 bit analogue-to-digital converter and were band-pass filtered offline between 1–45 Hz (4th order Butterworth characteristic). Additionally, a notch filter (3rd order) was used to suppress contributions at the line frequency (50 Hz). We visually inspected all recordings for strong artefacts such as subject movements, amplifier saturation, or stimulation artefacts. Such data were excluded from further analyses.

We used a sliding-window approach[44–46] to calculate a synchronisation index r_{ij} (mean phase coherence[47]) between phase time series (derived adaptively with Hilbert transform[48]) from all pairs of brain regions (i, j) sampled by the EEG electrodes. Non-overlapping windows had duration of 20 s (5120 data points), which represents a compromise between the required statistical accuracy for the calculation of r_{ij} and approximate stationarity within a window length.

The synchronisation index serves as an indicator for the strength of functional interactions in the epileptic brain network[45] and is confined to the unit interval: $r_{ij} = 1$ indicates fully phase-synchronised brain regions and $r_{ij} = 0$ indexes no phase synchronisation. For subsequent analyses, we associated the sampled brain regions with network vertices and the calculated phase synchronisation indices between any pair of vertices with network edges. This resulted in a time-dependent sequence of weighted and fully connected brain networks.

Network characteristics. In addition to global synchronisation level R (mean over all non-redundant pairwise synchronisation indices), we assessed four relevant global characteristics for each network that we derived from the time-resolved synchronisation analysis of the 3-h EEG recording prior to (phase 1), during (phase 2), and after taVNS (phase 3): average shortest path length L, average clustering coefficient C, synchronisability S, and assortativity A. In order to remove possible transient effects, we neglected data from the first and last 15 min of each phase.

The average shortest path length L is defined as the average number of steps along the shortest paths for all possible pairs of network vertices. For our weighted networks, we defined the 'length' of a path between a pair of vertices as the inverse of the weight of the edge that connects the vertices[20] and used an algorithm proposed by Dijkstra[49] to compute L. The clustering coefficient is a measure of the degree to which vertices in a network tend to cluster together. We made use of a definition of the clustering coefficient in a weighted network[50] and calculated the average clustering coefficient C as the mean of clustering coefficients computed for all vertices. Synchronisability S is a measure of the stability of the network's synchronised state[51,52]. We computed S from the ratio of the largest and smallest non-vanishing eigenvalue that we calculated for the network's Laplacian[53]. To assess assortativity A of the networks[54], we estimated the Pearson correlation coefficient between the degrees of vertices at both ends of an edge[55]. To this end, we derived a connected binary network from the weighted network by thresholding thereby requiring a constant edge density. A is confined to the interval $[-1, 1]$ by definition. Positive (negative) values of A indicate an assortative (disassortative) network.

Statistical analyses. Differences between network characteristics from the three phases (phase 1: pre-stimulation; phase 2: during stimulation; phase 3: post-stimulation; see Fig. 1) were investigated on a per-subject basis using the Mann–Whitney U-test (phase 1 vs. phase 2, phase 1 vs. phase 3, and phase 2 vs. phase 3). For

downstream network analyses, we only considered data from subjects for whom we attained significant differences after Bonferroni correction ($p < 0.05$). Group level (all subjects) differences between neuropsychological variables from the phases prior to and after the EEG recording (NP1 vs. NP2; see Fig. 1) were investigated using the Mann–Whitney U-test ($p < 0.05$). Finally, we probed for possible relationships between the aforementioned changes in neuropsychological variables and (a) network characteristics (temporal means) from the three phases and (b) relative changes of network characteristics between the three phases (relative changes calculated as $\Delta = (M_l - M_k)/M_k$, where M_k and M_l denote placeholders for the temporal means of the respective characteristics from phase k and phase l). Relationships were deemed significant after Bonferroni correction (Pearson correlation coefficient; $p < 0.05$).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available as they contain information that could compromise the privacy of research participants.

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Competing interests

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Additional information

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REVIEW

Efficacy and safety of VNS therapy or continued medication management for treatment of adults with drug-resistant epilepsy: systematic review and meta-analysis

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Abstract

Vagus nerve stimulation (VNS) Therapy® is an adjunctive neurostimulation treatment for people with drug-resistant epilepsy (DRE) who are unwilling to undergo resective surgery, have had unsuccessful surgery or are unsuitable for surgery. A systematic review and meta-analysis were conducted to determine the treatment effects of VNS Therapy as an adjunct to anti-seizure medications (ASMs) for the management of adults with DRE. A literature search was performed in August 2020 of the Medline®, Medline® Epub Ahead of Print, Embase, and the Cochrane library databases. Outcomes examined included reduction in seizure frequency, seizure freedom, ASM load, discontinuations, and serious adverse events (SAEs). Comparators included best medical practice, ASMs, low-stimulation or sham VNS Therapy. Four RCTs and six comparative observational studies were identified for inclusion. Against comparators, individuals treated with VNS had a significantly better odds of experiencing a ≥ 50% reduction in seizure frequency (OR: 2.27 [95% CI 1.47, 3.51]; $p = 0.0002$), a ≥ 75% reduction in seizure frequency (OR: 3.56 [95% CI 1.59, 7.98]; $p = 0.002$) and a reduced risk for increased ASM load (risk ratio: 0.36 [95% CI 0.21, 0.62]; $p = 0.0002$). There was no difference in the odds of discontinuation or the rate of SAEs between VNS versus comparators. This meta-analysis demonstrated the benefits of VNS Therapy in people with DRE, which included improvement in seizure frequency without an increase in the rate of SAEs or discontinuations, thereby supporting the consideration of VNS Therapy for people who are not responding to ASMs and those unsuitable or unwilling to undergo surgery.

Keywords Anti-seizure medication · VNS therapy · Meta-analysis · Drug-resistant epilepsy · Seizure frequency

Introduction

Epilepsy is a common neurological condition, affecting approximately 50 million people globally [1]. At least 30% exhibit drug-resistant epilepsy (DRE) and continue to suffer seizures despite treatment [2]. DRE is defined by the International League Against Epilepsy (ILAE) as failure of adequate trials of two tolerated, appropriately chosen and used anti-seizure medication (ASM) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [3].

People with DRE experience significantly more comorbidities, including depression, seizure-related injuries, and neurological deficits than those without epilepsy or with epilepsy that responds to treatment [4, 5], and have significantly higher mortality risk [6, 7]. DRE is also associated with sudden unexplained death in epilepsy (SUDEP) which represents a major cause of death in this population [8–10].

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People with DRE have substantially higher healthcare costs than those who are seizure-free, including costs associated with medical investigations, treatment costs, emergency room visits, hospitalisations, and outpatient care [18–20]. In addition, people with DRE frequently report feeling stigmatised because of their epilepsy [11].

It has been reported that greater than 30% of people with DRE remain uncontrolled despite the availability of new ASMs, and this statistic has not changed over the last 20 years. [12, 13]. For people who fail to experience sufficient seizure reduction with pharmacologic therapy, alternative approaches include epilepsy brain surgery [14], diet modification [15], and neurostimulation devices [16–19], including Vagus Nerve Stimulation Therapy® (VNS Therapy®) [20, 21].

While for many people with DRE brain surgery can be curative and result in seizure freedom, with up to 52% of people remaining seizure-free (apart from simple partial seizures) 5 years post-intervention [22, 23]. However, not all individuals are suitable candidates, and uptake of surgery is limited by hesitancy, in part due to fears of postoperative permanent neurological deficits [24].

VNS Therapy represents a commonly used neurostimulation option for people with DRE who do not wish to undergo cranial surgery or laser interstitial thermal ablation, who have had unsuccessful surgery or are not suitable for surgery (including individuals with intellectual impairment who may be unable to understand and consent to a non-reversible procedure) [25–27]. VNS is a minimally invasive extracranial device which delivers mild, intermittent electrical pulses to the vagus nerve which then stimulates areas in the brain responsible for seizures [28, 29]. This results in a reduction in seizure frequency [20, 21]. VNS Therapy® has been in clinical use in Europe since 1994 [30] and in the USA since 1997 [31].

This systematic literature review (SLR) and meta-analysis examined the treatment effects of VNS Therapy at up to 2 years as an adjunct to ASMs for the management of adults with DRE based on the most up-to-date evidence from randomised controlled trials (RCTs) and comparative observational studies.

Materials and methods

SLR

An SLR was conducted on the 25th of August 2020 (in alignment with the Preferred Reporting Items for Systematic reviews and Meta-Analyses [PRISMA] checklist) [32] to identify relevant clinical studies (RCTs and observational comparative studies) comparing VNS Therapy as an adjunct to ASMs with relevant comparator arms in adults with DRE followed by a meta-analysis to determine treatment effects for several efficacy and safety outcomes.

The SLR searched the electronic databases of Medline®, Medline® Epub Ahead of Print (In-Process & Other Non-Indexed Citations), Embase, and the Cochrane library to identify relevant clinical studies (RCTs, controlled clinical studies, and prospective registries) examining VNS Therapy and other interventions of interest for the management of patients with DRE. Additional searches of congress proceedings from the past 3 years (American Epilepsy Society [AES], Congress of Neurological Surgeons [CNS] Annual Meeting, European Congress on Epileptology [ECE], International Epilepsy Congress [IEC], International Neuromodulation Society [INS] Congress), reference lists of included publications, and Health Technology Assessment (HTA) bodies were conducted to identify relevant evidence. Search terms are listed in the Supplementary Materials. Citations were screened by a single analyst and independently checked by a second analyst; any discrepancies were resolved by consensus. Outcome data were extracted to a Microsoft® Excel spreadsheet.

For this analysis, the eligibility criteria included comparative clinical studies of VNS Therapy for the management of DRE conducted predominantly in an adult population (i.e., > 50% of individuals were aged ≥ 18 years). Eligible comparators to VNS Therapy were: (1) best medical practice (BMP), (2) continuation of stable ASM regimen, (3) addition of ASM, and (4) low-stimulation VNS Therapy (parameters defined in Table 3).

Data collection and risk of bias assessment

General patient/participant demographics were extracted, such as age at time of implant, sex, type of seizure and baseline seizure frequency. Outcomes of interest included reduction in seizure frequency, seizure freedom, ASM load, discontinuations, and serious adverse events (SAEs).

Quality (risk of bias) assessment of RCTs was conducted using the seven-criteria checklist provided in Sect. 2.5 of the National Institute for Health and Care Excellence (NICE) single technology appraisal (STA) user guide for RCTs [33]. Observational studies were assessed using the quality assessment tool for quantitative studies of the Effective Public Health Practice Project (EPHPP) [34].

Meta-analysis

Evidence synthesis was conducted via pairwise meta-analyses based on RCT and comparative observational studies. While observational comparative evidence is of lower quality compared with RCTs due to the inherent bias within such studies, their inclusion was deemed appropriate as observational comparative studies provide longer follow-up

compared with RCTs. Pairwise meta-analyses were conducted for the outcomes of interest previously described. For one RCT (PuLsE) [35], which reported outcomes up to 2-year post-surgery, the outcome results were restricted to the 12-month timepoint. The 12-month results were included in the meta-analysis. Outcomes for this study were restricted to 12 months to facilitate data comparisons as all other RCTs included in the meta-analysis had shorter followups (range: 3.5–6 months).

Statistical analysis

Evidence synthesis was conducted via pairwise meta-analyses based on RCT and comparative observational studies where available. The pairwise meta-analyses were conducted in RevMan 5.3. Heterogeneity was assessed using the chi-squared and I-squared statistics. Results were presented as an odds ratio (OR) or weighted mean difference with 95% confidence intervals (CIs).

Results

SLR

RCTs and comparative observational studies

A total of 48 publications (on 30 unique studies, see Supplementary Materials Table 1) were identified for potential inclusion. In total, 38 VNS Therapy studies did not meet eligibility criteria for inclusion in this meta-analysis (due to publications including non-relevant comparators, no outcomes of interest or publications were superseded by a linked publication); 10 studies were identified for inclusion (four RCT studies [4 unique publications] and six comparative observational studies [5 unique publications]) (Fig. 1). The publication dates ranged between 1993 and 2015.

Four primary study publications from four RCTs in an adult population were included in the analysis; 13 publications linked to these RCTs were excluded as they did not report outcomes of interest or were superseded by the primary study publication [36–47]. A single RCT study (with two linked publications; see Supplementary Materials Table 1) was excluded due to unclear reporting of the enrolled population (i.e., proportion of adults) [48, 49]. A total of 12 adult comparative observational study publications were excluded for the following reasons: no comparator ($n=4$) [50–53], population of interest ($n=2$) [54, 55], reported no outcomes of interest (n = 5)[56–60] and superseded by a linked primary publication ($n=1$)[61].

Study and participant characteristics

Study design and baseline participant characteristics of the VNS Therapy studies are shown in Tables 1 and 2. The study duration ranged from 3 to 4.5 months for the majority of RCTs [20, 21, 62], with one RCT study lasting 24 months [35]. The study duration for comparative observational studies was typically > 12 months (range: 3–32 months) [63–68]. Where reported, the mean participant age ranged 32–41 years for the RCT studies [20, 21, 35, 62] and 25–40 years for comparative observational studies. Disease duration was only reported by half of the studies included ($n=5$), with the mean duration ranging between 20 and 23 years for RCT studies [20, 21] and 17–26 years for comparative observational studies [63, 66, 68]. Mean seizure frequency ranged from 0.6–1.7 and 0.1–3.5 seizures per day for RCT and non-comparative observational studies, respectively. The mean number of drugs used ranged between 2 and 3 for both RCT [20, 21, 35] and comparative observational studies [64–66, 68]. Three studies compared a low-stimulation setting (control arm) plus background ASMs with a high-stimulation setting; the difference between the low- and high-stimulation parameters is provided in Table 3. Rationale for using the low-stimulation included the facilitation of titration, ethical reasons, inclusion of an active control group and to permit a double-blind trial design [20, 62, 69]. The majority of studies ($n=7$) compared VNS Therapy with a continuation of the participants' current ASM regimen; only one comparative observational study reported the type of ASMs participants were taking [65]. None of the included studies made a specific comparison between VNS Therapy and the latest generation of ASMs (e.g., those licensed in the last two decades [i.e., lacosamide, cannabidiol, brivaracetam, perampanel etc.]). VNS is an option for people with DRE who are unsuitable for epilepsy surgery, have had unsuccessful surgery or are unwilling to undergo resective surgery. Only three out of ten of the included studies provided rationale for the use of VNS, reasons included unsuitability for surgery and patient choice [63, 64, 66].

Participants experiencing ≥ 50% reduction in seizure frequency

A total of six studies (three RCTs and three comparative observational studies) were included in the analysis. Overall, the pooled odds ratio (based on the results of RCTs and comparative observational studies) for experiencing ≥ 50% reduction in seizure frequency was statistically significantly greater in adult participants undergoing VNS Therapy compared with low stim VNS Therapy/BMP/ASM (OR: 2.27

Table 1 Summary of included RCTs

Author/Publication	Location	Treatment length	Duration of follow-up	Comparators	Sample size, *n*	Age at implant mean (SD [range])	Sex, F (*n* [%])	Mean duration of disease, years	Mean no. of ASMs used at baseline	Seizure types,† *n* (%‡)	Seizure frequency	Outcomes assessed
Ryvlin [35] (PuLsE)§	Canada, Europe	2 years	2 years	VNS + BMP	54	38 ± 13	24 (50)	NR	3.5 (SD: ± 1.17)	Structural/metabolic: 26 (54) Unknown: 22 (46)	Median: 5 per week (range: 1 to 123)	Seizure frequency (including ≥ 50%) HRQoL ASM usage Adverse events
				BMP (ASM)	58	41 ± 11	21 (44)		3.2 (SD: ± 1.22)	Structural/metabolic: 26 (54) Unknown: 22 (46)	Median: 4 per week (range: 1 to 42)	
E-05 (Handforth [20])§	US	3 months	3.5–4 months	VNS high stim	95	32.1 (10.8 [13–54])	46 (48.4)	23	2.2 (SD: ± 0.7)	CPS or partial + secondarily generalised, ± other seizure types	Mean: 1.59 per day (SD ± 1.96) Median: 0.58 per day	Seizure frequency (including ≥ 50%, ≥ 75% and seizure free) ASM usage Quality of life Adverse events Discontinuations
				VNS low stim	103	34.2 (10.1 [15–60])	59 (57.3)		2.1 (SD: ± 0.7)		Mean: 0.97 per day (SD ± 0.94) Median: 0.51 per day	
E-03 (Salinsky [21]) §	Europe, North America	3 months	3.5–4 months	VNS high stim	54	33.1 (NR)	21 (39)	23.1	2.09	SPS: 24 (44.4%) CPS: 50 (92.6%) Partial secondarily generalised: 38 (70.4%)	Mean 1.49 per day (SD: NR) Median: 0.73 per day	Seizure frequency (including ≥ 50%, ≥ 75% and seizure free) Adverse events
				VNS low stim	60	33.5 (NR)	22 (37)	20.0	2.08	SPS: 25 (41.6%) CPS: 58 (96.6%) Partial secondarily generalised: 33 (55.0%)	Mean 1.71 per day (SD: NR) Median: 0.82 per day	
Landy [62]	US	3–4.5 months	6.5 months	VNS high stim	5	NR	NR	NR	NR	NR	NR	Seizure frequency Adverse events
				VNS low stim	4							

Abbreviations: *ASM* anti-seizure medication, *BMP* best medical practice, *CPS* complex partial seizures, *HRQoL* health-related quality of life, *NR* not reported, *RCT* randomised controlled trial, *SD* standard deviation, *SPS* simple partial seizures, *VNS* vagus nerve stimulation

†May be counted in more than one type; ‡Where applicable; §Cyberonics-sponsored VNS study (Cyberonics is owned by LivaNova)

Table 2 Summary of included comparative observational studies

Author / Publication	Location	Treatment length	Comparators	Duration of Follow-up	Sample size, n	Age at implant mean (SD [range])	Sex, F (*n* [%])	Mean duration of disease	Mean no. of ASMs used	Seizure types,† *n* (%‡)	Seizure frequency	Outcomes Assessed
Gonen [64] (Comparative retrospective observational study)	Israel	≥ 1 year	VNS + ASM	5.67 years	33	> 18 years of age	14 (42.4)	NR	2.91 (SD: ± 0.95)	NR	Mean: 3.52 per day (SD 0.67)	Seizure frequency, ASM usage
			ASM	4.04 years	47		26 (55.3)		2.32 (SD: ± 0.98)		Mean: 3.15 per day (SD 0.72)	
Hoppe [66] (Comparative, Case control)§	Germany	> 2 years	VNS + BMP (ASM)	6.8 years (SD 2.1, range 2–13)	20	39.8 (SD: 10.2)	8 (40)	25.7 (SD: 13.4)	2.47 (SD: ± 0.77)	SPS: 8 (40%) CPS: 18 (90%) SGS: 10 (50%)	Mean: 68.4 (SD 206.3) per month	Seizure frequency, ASM use and tolerability, VNS tolerability HRQoL, ASM use, adverse events
			BMP (ASM)		20	39 (SD: 8.5)	8 (40)	21.0 (SD: 9.2)	2.24 (SD: ± 0.44)	SPS: 7 (35%) CPD: 17 (85%) SPS: 12 (60%)	Mean 8.2 (SD 10.4) per month	
Marrosu [65] (Comparative Prospective case control)	Italy	1 year	VNS implant	1 year	10	33.1 (23–44)	4 (40)	NR	1.9	CPS	Mean 156 (range: 98–212) per trimester	Seizure frequency, GRD distribution
			No implant		7	30.8 (21–42)	3 (43)		1.9		Mean 150 (range 88–206) per trimester	

Table 2 (continued)

Author / Publication	Location	Treatment length	Comparators	Duration of Follow-up	Sample size, n	Age at implant mean (SD [range])	Sex, F (*n* [%])	Mean duration of disease	Mean no. of ASMs used	Seizure types,† *n* (%‡)	Seizure frequency	Outcomes Assessed
Boon [63] (Comparative Prospective Cohort)	Belgium	Average 26 months [range 12–57 months]	VNS + ASM	29 months (range: 12–57)	25	31 years (range: 12–49 years)	NR	21 years (range: 2–50 years)	NR	SPS + SG: 15 (60%) CPS + SG/SPS: 3 (12%) CPS + SG/atonic: 2 (8%) CPS: 5 (20%)	Mean: 21 per month (range: 2 to 180)	Epilepsy-related direct medical costs, Seizure frequency Number and dosage of ASMs, Number of hospital admission days clinic visits and laboratory tests
			Surgery	28 months (range, 12–54)	35	32 (range: 10–60 years)				SPS + SG: 1 (3%) CPS + SG: 17 (49%) CPS: 14 (40%) GTC: 1 (3%) CPS/atonic: 1 (3%) CPS + SG/atonic: 1 (3%)	Mean: 6 per month (range: 1 to 17)	
			ASM only	25 (range: 12–48)	24	34 years (range: 5–71 years)				CPS: 7 (29%) CPS + SG: 10 (42%) SPS/CPS + SG: 1 (4%) GTC: 2 (8%) SPS/CPS: 2 (8%) CPS + SG/psych: 2 (8%)	Mean: 12 per month (range: 1 to 30)	
Tatum [68] Comparative Prospective case control)	US	13.2 months	VNS	13.2 months (NR)	21	24.8 (range: 4–51)	9 (43)	17.0 (range: 4–45)	2.81 (range: 1–5)	NR	NR	Seizure frequency, ASM dose and usage, QoL
			Control (ASM)		21	26.1 (5–57)	12 (57)	19.9 (range: 3–46)	2.38 (range: 1–4)			

Table 2 (continued)

Author / Publication	Location	Treatment length	Comparators	Duration of Follow-up	Sample size, n	Age at implant mean (SD [range])	Sex, F (*n* [%])	Mean duration of disease	Mean no. of ASMs used	Seizure types,† *n* (%‡)	Seizure frequency	Outcomes Assessed
Harden [67] (Comparative—Prospective cohort)§	US	3 months	VNS	3 months (SD 1.7)	20	39 (SD: 9.1 [range: 20–58])	14 (70)	NR	NR	CPS: 12 (60%) CP + secondarily GTC: 5 (25%) Primary GTC: 3 (15%)	Mean: 16.2 (SD 19.4) per month	Seizure frequency, Medication side effects, HRQoL
			BMP (ASM)	3.8 months (SD 1.6)	20	40.2 (SD: 13.3 [range: 24–69])	14 (70)			CPS: 10 (50%) Secondarily GTC: 5 (25%) CP + Secondarily GTC: 5 (25%)	Mean: 3.2 (SD 7.4) per month	

Abbreviations: *ASM* anti-seizure medication, *BMP* best medical practice, *CPS* complex partial seizures, *$GABA_A$* gamma-aminobutyric acid, *GRD* $GABA_A$ receptor density, *GTC* generalized tonic–clonic seizures, *HRQoL* health-related quality of life, *NR* not reported, *psych* psychogenic nonepileptic seizures, *RCT* randomised controlled trial, *SD* standard deviation, *SG* secondary generalisation, *SPS* simple partial seizures, *SZ* seizure, *VNS* vagus nerve stimulation

†May be counted in more than one type; ‡Where applicable; §Cyberonics-sponsored VNS study (Cyberonics is owned by LivaNova)

Table 3 Summary of high and low stimulation parameters

VNS therapy parameter	Landy 1993		E-03 (Salinsky 1995)		E-05 (Handforth 1998)	
Device setting	Low	High	Low	High	Low	High
Output current (mA)	0.5–3.0	0.5–3.0	0.25–2.75	0.25–3.0	1.2 (avg)	1.3 (avg)
Signal frequency (Hz)	1–2	20–50	1–2	20–50	1	30
Pulse width (μsec)	130	500	130	500	130	500
Signal on time (sec)	30	30–90	30	30–90	30	30
Signal off time (min)	60–180	5–10	60–180	5–10	180	5

[95% CI 1.47, 3.51]; $p=0.0002$). A similar statistically significant result was observed when results were pooled by study type (RCTs: OR 1.93 [95% CI 1.16, 3.20], $p=0.01$; observational comparative studies: OR 3.64 [95% CI 1.51, 8.73], $p=0.004$). Low levels of heterogeneity were observed between studies (Fig. 2).

Participants experiencing ≥ 75% reduction in seizure frequency

Five studies (two RCTs and three comparative observational studies) were included in the analysis. In the pooled analysis, the odds of experiencing a ≥ 75% reduction in seizure frequency were more than three times greater in adult participants undergoing VNS Therapy compared with low-stimulation VNS Therapy/ASM (OR: 3.56 [95% CI 1.59, 7.98]; $p=0.002$). A similar statistically significant result was observed for pooled RCT studies (OR 5.54 [95% CI 1.56, 19.67]; $p=0.008$); pooled results for comparative observational studies were not statistically significant (OR: 2.43 [95% CI 0.83, 7.11]; $p=0.11$). A trend for a greater VNS Therapy treatment effect in RCTs at a shorter follow-up time (OR 5.54 [95% CI 1.56, 19.67]) compared with observational data at a longer follow-up time (OR: 2.43 [95% CI 0.83, 7.11]) was observed. Low levels of heterogeneity were observed between studies (Fig. 3).

Participants that are seizure free

A total of six studies (two RCTs and four comparative observational studies) were included in the analysis. There is no difference in the odds of freedom from seizures in adult participants undergoing VNS Therapy compared with low-stimulation VNS Therapy/ASM (OR: 0.82 [95% CI 0.37, 1.84]; $p=0.64$). On a study level, results were inconsistent across RCTs and comparative observational studies. Moderate levels of heterogeneity were observed between studies and there were large levels of uncertainty across the trial estimates due to low event numbers (Fig. 4).

Mean change from baseline in seizure frequency

Three RCT studies were included in the analysis. VNS Therapy was associated with a statistically significant decrease in the percentage change from baseline in seizures compared with low VNS Therapy (CFB: −18.26% [95% CI −20.12, −16.41]; $p<0.00001$). Consistent results were observed across the three RCTs reporting on this outcome and low levels of heterogeneity were observed (Fig. 5).

ASM load

The analysis for ASM load was based on two studies (one RCTs and one comparative observational studies). In the pooled analysis, participants undergoing VNS Therapy had a significant reduction in the risk of having an increased ASM load when compared with BMP or control (case-matched participants on ASMs) (risk ratio [RR]: 0.36 [95% CI 0.21, 0.62]; $p=0.0002$). Similarly, pooled analysis indicated that participants undergoing VNS Therapy had a significant reduction in the risk of adding one or more new ASMs during treatment when compared with BMP or control (case-matched participants on ASMs) (RR: 0.28 [95% CI 0.13, 0.58]; $p=0.0007$). Results from a single RCT and comparative observational study formed the pooled analysis for both outcomes; low levels of heterogeneity were observed between studies. Separately, both studies reported significant differences for both outcomes favouring VNS Therapy (see Figs. 6 and 7).

VNS Therapy discontinuation

The discontinuation analysis included two RCT studies; no difference in the odds of discontinuing VNS Therapy treatment in adult participants undergoing VNS Therapy versus low-stimulation VNS Therapy/BMP was observed (OR: 1.31 [95% CI 0.51, 3.36]; $p=0.57$). Consistent

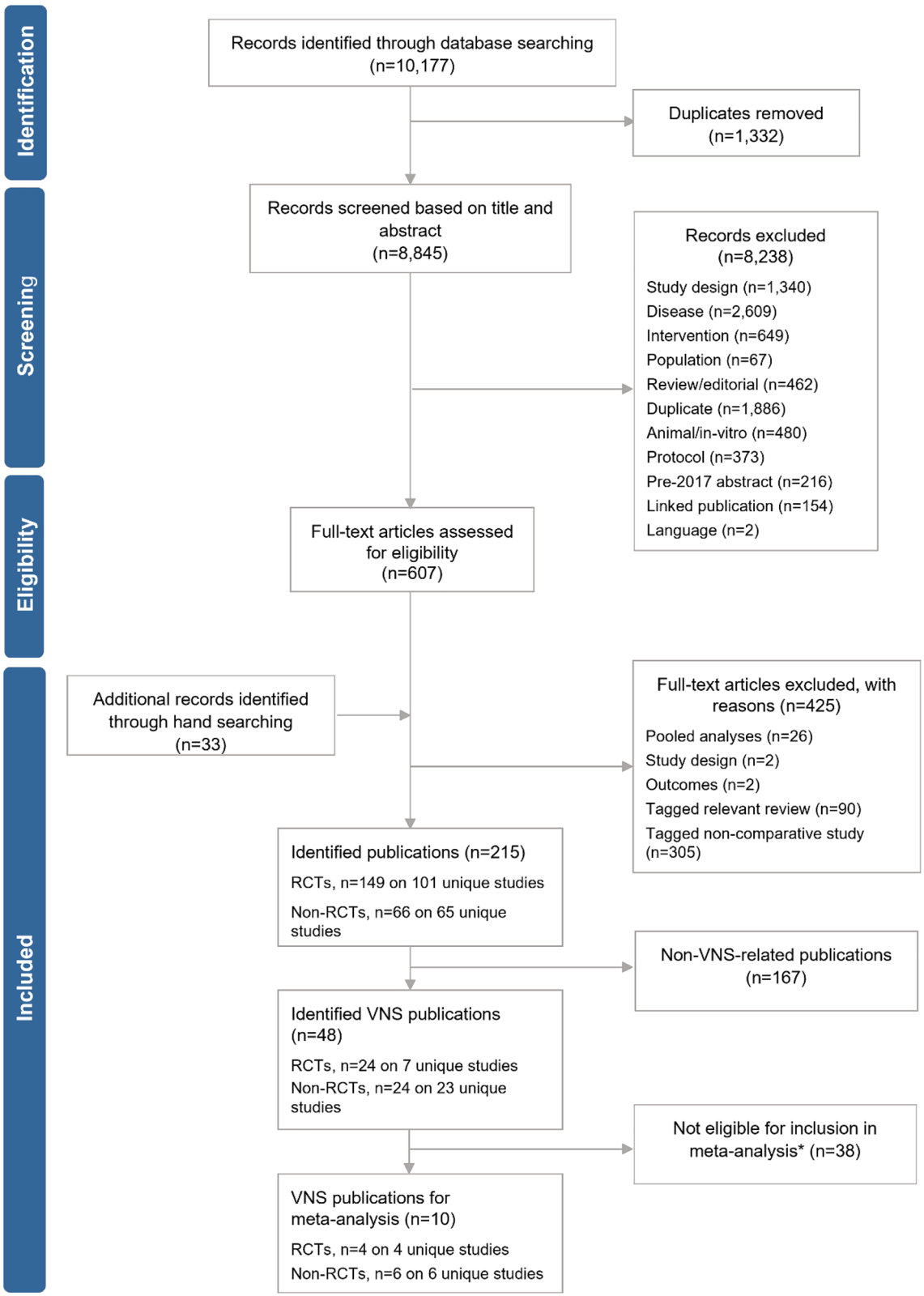

Fig. 1 PRISMA flow diagram. Abbreviations: *RCT* randomised controlled trial, *VNS*, Vagus Nerve Stimulation. *Primarily due to publications including non-relevant comparators, no outcomes of interest or publications were superseded by a linked publication

results were observed across the two RCTs reporting on this outcome. Low levels of heterogeneity were observed between studies and there were large levels of uncertainty across the trial estimates due to low event numbers (Fig. 8).

SAEs

A single RCT study was included in the SAE analysis. No difference in the odds of an SAE in adult participants undergoing VNS Therapy compared with BMP was observed (OR: 1.87 [95% CI 0.42, 8.24]; $p = 0.41$) (Fig. 9).

Discussion

This systematic review and meta-analysis demonstrated that in people with DRE, adjunctive high-stimulation VNS Therapy resulted in statistically significant reductions in seizure frequency without increasing the rate of SAEs or discontinuations when compared with adjunctive low-stimulation VNS Therapy/ASM/best medical practice. This evidence validates the consideration of VNS Therapy for people who respond poorly to ASMs, or those who are unsuitable for or unwilling to undergo any cranial procedure. Furthermore, the results of this study are in agreement with the current guideline recommendations for the use of VNS Therapy in adults [27, 70–72].

While VNS Therapy resulted in a statistically significant outcomes at the pooled level, some were not statistically significant at the trial level. For the ≥ 50% reduction in seizure frequency outcome, only a single trial was statistically significant at the trial level (E03). The other studies (E-05 and PuLsE) were not statistically significant likely due to the low number of participants involved and wide confidence intervals observed. For the ≥ 75% reduction in seizure frequency outcome, the pooled analysis (RCTs and comparative observational studies) and pooled RCT analysis both reported a statistically significant benefit of VNS Therapy. However, the pooled results for the comparative observational studies were not statistically significant, possibly due to study heterogeneity (specifically participant number, study length) and different magnitudes of treatment effects.

There is no difference in the odds of complete freedom from seizures for adult participants undergoing VNS Therapy versus low-stimulation VNS Therapy/ASM. This result reflects current evidence in the literature, with other studies reporting that people with DRE undergoing VNS Therapy have a low rate of seizure freedom, despite response and seizure freedom rates increasing over time [73]. It must be noted that no events for seizure freedom were observed in RCT studies included in this analysis, with seizure freedom events only recorded in the comparative observational studies, which have a longer follow-up. Seizure freedom, however, was observed in 15 of 273 individuals with DRE.

The beneficial impact of VNS Therapy on ASM load was limited to two studies (PuLsE RCT and Tatum 2001), indicating that participants are less likely to require new ASMs or have an increased ASM load compared with BMP or control (case-matched participants on ASMs). When viewed alongside other seizure control outcomes from this analysis, the evidence suggests that VNS Therapy may permit

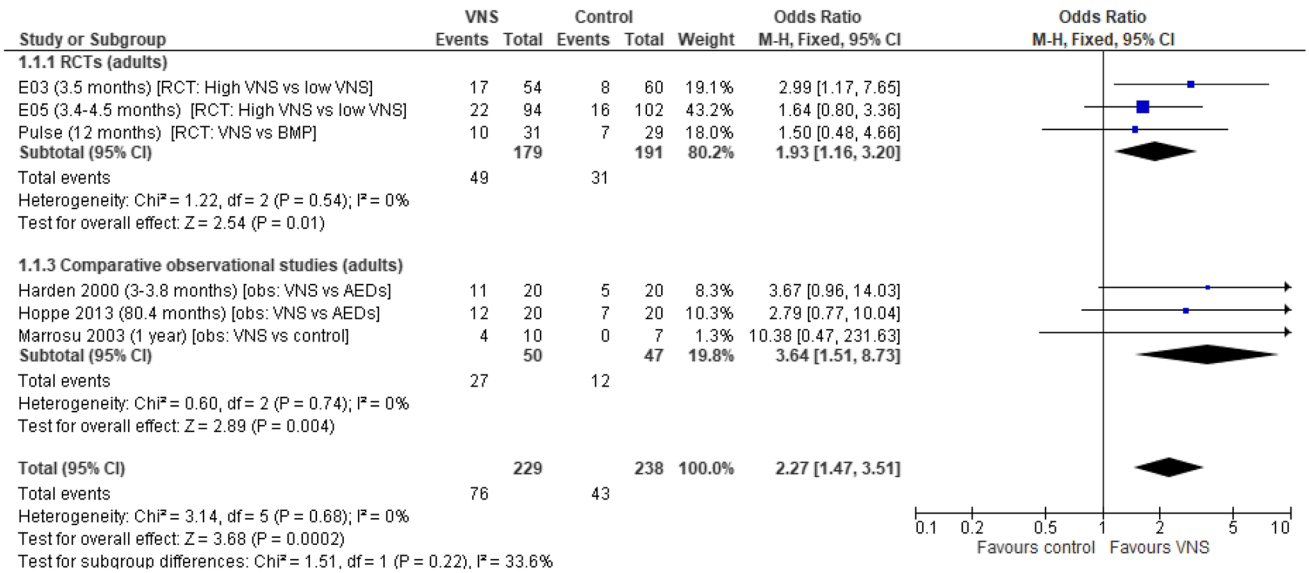

Fig. 2 Participants experiencing ≥ 50% reduction in seizure frequency. Abbreviations: *ASM* antiepileptic drug, *BMP* best medical practice, *CI* confidence interval, *RCT* randomised controlled trial, *SD* standard deviations, *VNS* vagus nerve stimulation

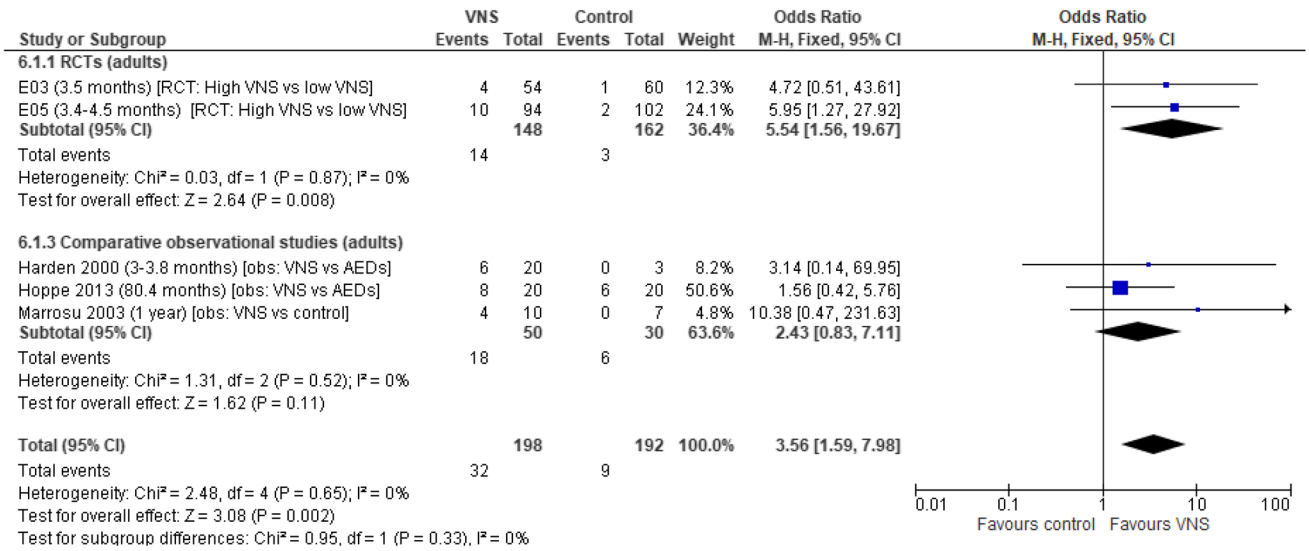

Fig. 3 Participants experiencing ≥ 75% reduction in seizure frequency. Abbreviations: *ASM* antiepileptic drug, *CI* confidence interval, *RCT* randomised controlled trial, *SD* standard deviations, *VNS* vagus nerve stimulation

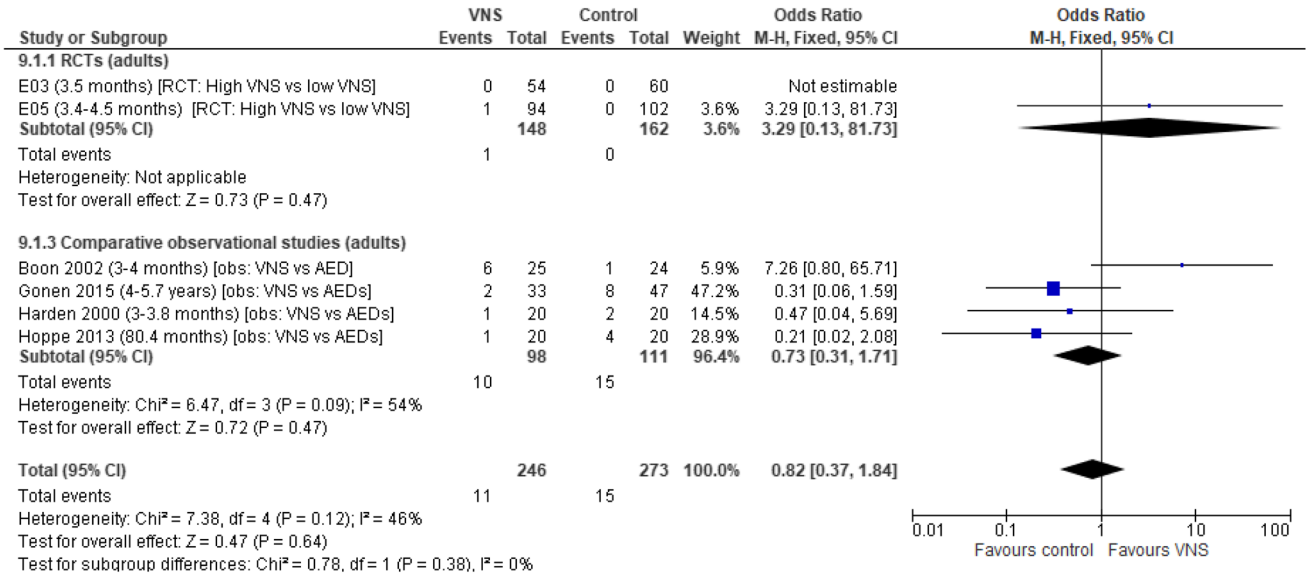

Fig. 4 Seizure-free participants. Abbreviations: *ASM* antiepileptic drug, *CI* confidence interval, *RCT* randomised controlled trial, *SD* standard deviation, *VNS* Vagus Nerve Stimulation

the reduction in concomitant ASMs without loss of seizure control. A lower drug burden is clinically important, because excessive drug load may be associated with decreased tolerability, and may consequently reduce the likelihood of seizure freedom [74]. Furthermore, certain ASMs are linked with a range of metabolic consequences that can adversely affect bone, lipid, and gonadal steroid metabolism. Consequently, reducing the drug burden may lower the risk of such complications [75]. Reductions in ASM load may also improve participant QoL, as a greater number of ASMs is a significant predictor of poor QoL [76]. In addition, studies have shown that seizure frequency in people with DRE was one of the most important factors contributing to patient QoL [77, 78]. Consequently, a reduction in seizures and their frequency may translate into QoL benefits. Of note, several studies which investigated use of VNS Therapy in individuals with DRE report improvements in seizure control and also observed improvements in QoL [35, 67, 79].

VNS therapy has comparable safety outcomes, specifically for SAEs and discontinuations, when compared with

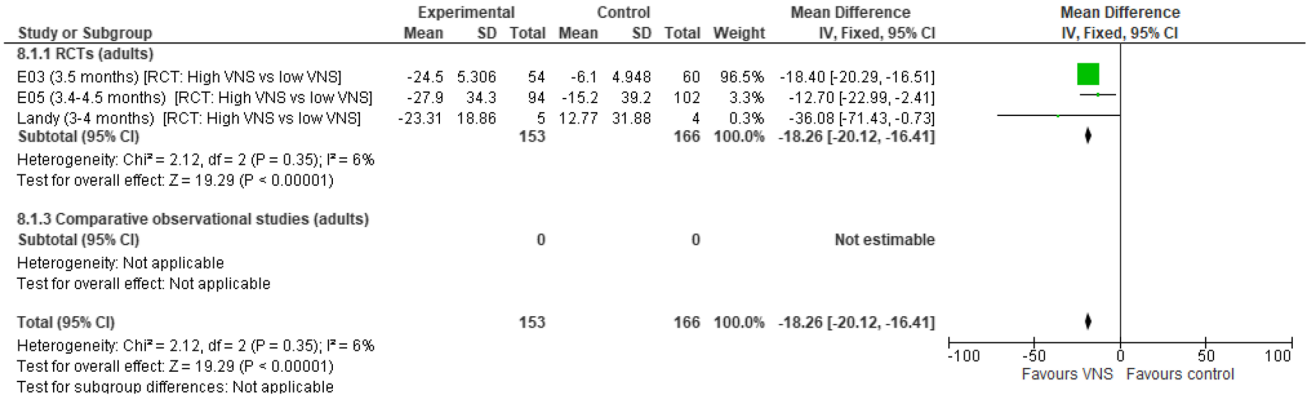

Fig. 5 Change from baseline in seizures, percentage. Abbreviations: *ASM* antiepileptic drug, *CI* confidence interval, *RCT* randomised controlled trial, *SD* standard deviation, *VNS* Vagus Nerve Stimulation

low-stimulation VNS Therapy/best medical practice. There was no difference in the odds of discontinuing treatment in adult participants undergoing VNS Therapy versus low-stimulation VNS Therapy/best medical practice, and there was no difference in the odds of an SAE in adult participants undergoing VNS Therapy versus best medical practice. When viewed alongside the seizure control outcomes from this analysis, the safety evidence suggests that VNS Therapy may facilitate better seizure control without increasing the rate of discontinuation or SAEs compared with participants undergoing VNS Therapy versus low-stimulation VNS Therapy/best medical practice. The discontinuation analysis was based on two RCTs of different duration; 12 months (PuLsE) and 3.4–4.5 months (E-05). Of note, there was only a single event in the VNS Therapy and comparator arm for E-05 compared with 46 and 47 events in the VNS Therapy and comparator arm for PuLsE. The main reasons for discontinuation in E-05 were Cheyne–Stokes respiration ($n=1$), and a variety of unspecified symptoms ($n=1$). For PuLsE, the majority of study discontinuations in either treatment group were due to premature termination of the study by the sponsor, and there were no discontinuations due to AEs.

It must be noted that of the studies identified for the meta-analysis, there was only one RCT (PuLsE; which had its outcomes restricted to 12 months for the meta-analysis) [35] and two comparative observational studies [63, 64] which reported long-term outcomes (≥ 2 years). Consequently, this makes it difficult to determine the long-term benefits associated with VNS Therapy. However, there are non-comparative, single-arm studies of VNS Therapy in people with DRE which provide an insight into the long-term treatment effects of VNS Therapy. A retrospective analysis of 436 participants (predominantly adults) with DRE treated with

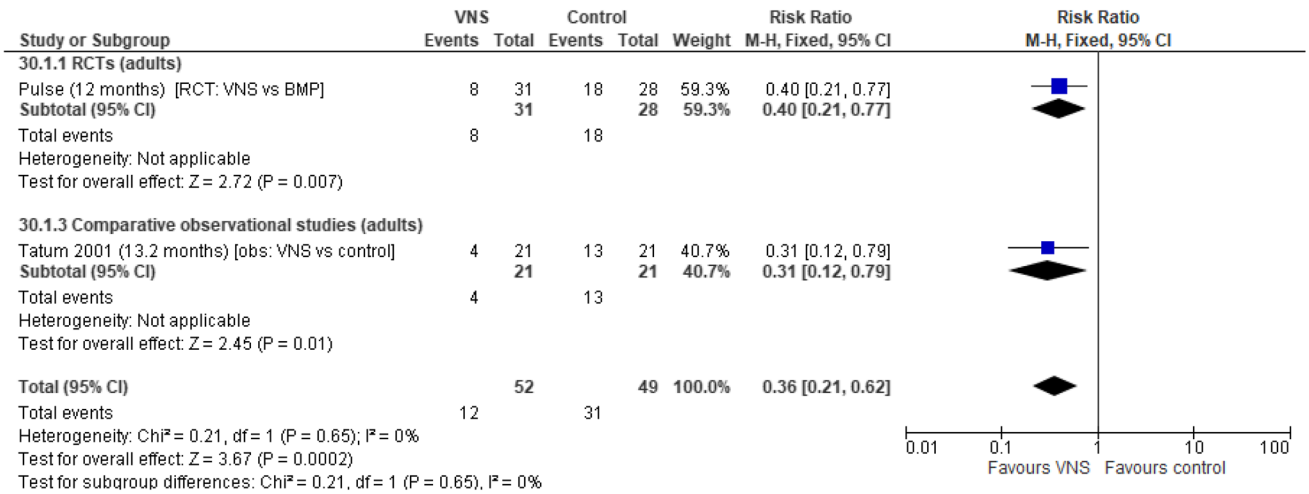

Fig. 6 Number of participants with increased ASM load. Abbreviations: *ASM* anti-seizure medication, *CI* confidence interval, *RCT* randomised controlled trial, *VNS* Vagus Nerve Stimulation

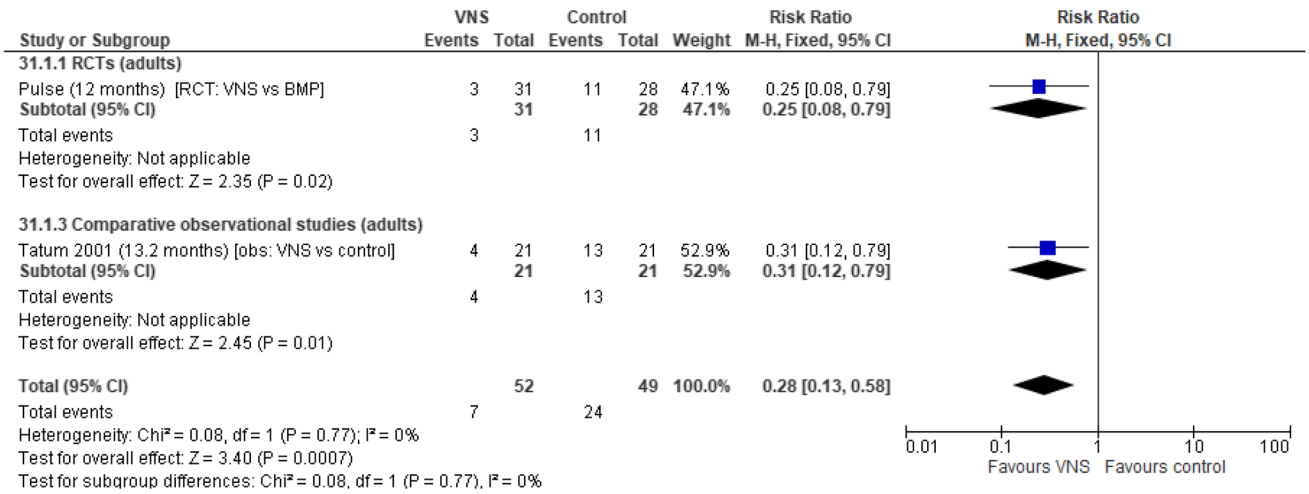

Fig. 7 Number of participants with one or more new ASMs. Abbreviations: *ASM* anti-seizure medication, *CI* confidence interval, *RCT* randomised controlled trial, *VNS* Vagus Nerve Stimulation

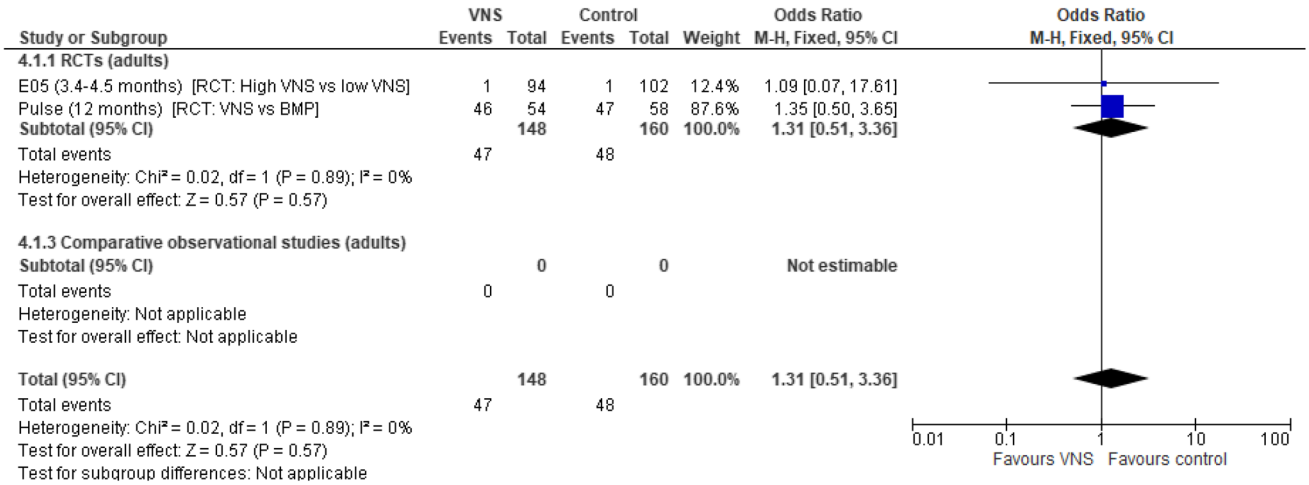

Fig. 8 Treatment discontinuations. Abbreviations: *ASM, anti-seizure medication; BMP, best medical practice; CI, confidence interval; RCT, randomised controlled trial; VNS, Vagus Nerve Stimulation*

VNS Therapy reported that participants achieved a mean seizure reduction of 55.8% after a mean follow-up of 5 years; 40.5 and 63.75% of participants achieved ≥ 75% seizure control and ≥ 50% seizure control, respectively [80]. The mean reduction in seizures continued to improve with duration; of those participants with > 10 years of follow-up ($n = 65$), the mean decrease in seizure frequency at last follow-up was 76.3% [81]. In addition, results from a prospective, open-label study of long-term VNS Therapy use (2 years) in individuals with DRE ($n = 40$) reported no significant safety events associated with Therapy and 95% (38/40) of patients remained on VNS Therapy for the study duration (one patient died [SUDEP] and the other was lost to follow-up after 1 year of treatment) [82]. The long-term benefits of VNS Therapy are reported in a number of other single-arm studies [83–85]. These results highlight the long-term benefits of VNS Therapy for people with DRE, but long-term comparative studies are required to determine if the benefits observed were solely due to VNS Therapy, or a potentially synergistic combination of ASM regimens and VNS Therapy. There are single-arm studies of shorter duration which support the meta-analysis results for VNS Therapy and ASM load. DeGiorgio et al. 2000 reported that participants with refractory epilepsy ($n = 195$) who were treated with VNS Therapy had a reduction in the mean number of ASMs, from 2.3 to 2.1 at the end of 12 months [46]. In addition, another study reported that up to 40% of participants experienced a decrease in the total dose of ASMs after 12 months of VNS Therapy [86]. While positive, these observations need to be supported by long-term comparative studies.

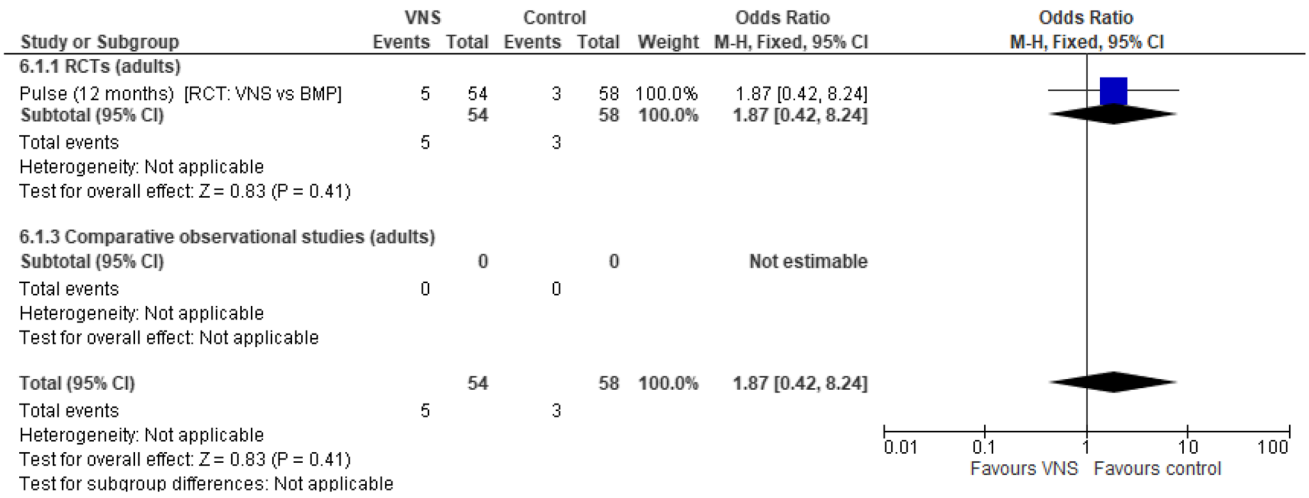

Fig. 9 SAEs. Abbreviations: *ASM* anti-seizure medication, *BMP* best medical practice, *CI* confidence interval, *RCT* randomised controlled trial, *SAE* serious adverse event, *VNS* Vagus Nerve Stimulation

As with all systematic reviews and meta-analyses, the results may need to be interpreted with caution due to certain limitations which include inconsistency across the trials for length of follow-up, greater treatment effects were often observed with observational comparative studies versus RCTs, and there were a very limited number of studies (≤ 2) for certain meta-analysis outcomes, specifically the discontinuation, SAE, and ASM load analyses. Of note, the number of studies identified for the meta-analysis was limited as the analysis focused on comparative observational studies and RCTs (which are the gold standard for generating estimates of relative treatment effects) which can be viewed as a strength of this analysis. Overall, there is limited high-quality evidence supporting the use of VNS Therapy in DRE. In addition, many trial-level estimates are associated with large levels of uncertainty (wide CIs) due to low participant and event numbers and in some instances single events are driving the direction of treatment effects. There was substantial variation in baseline seizure frequency reported by observational comparative studies (0.1–3.5 seizures per day). Seizure frequency in VNS Therapy participants and control participants were not comparable at baseline in the majority of reporting studies, with participants in the VNS Therapy arm having a greater baseline seizure frequency [63, 66, 67]. Another limitation of the analysis was the differences in VNS Therapy stimulation parameters across studies contributing to further heterogeneity amongst participant groups. In the early RCTs regulating stimulation parameters, the low-stimulation group was titrated to sensation and the high stimulation group to maximum tolerated stimulation. Subsequent studies have suggested this may not be necessary for optimal efficacy and may contribute to difficulties in tolerability. Finally, three of the VNS Therapy trials informing efficacy (E-03, E-05 and Landy 1993) did not compare VNS Therapy with ASM therapy only. These trials compared VNS Therapy at 'high stimulation' settings with a presumed sub-therapeutic 'low-stimulation' regimen; ASMs were given in both arms. Therapeutic VNS is driven by the generation of action potentials along the vagus nerve, which is a function of the strength-duration relationship [87]. It is reported in the literature that 1.5 mA at 130 µsec to 2.25 mA at 500 µsec is considered a therapeutic dose [20, 62, 69, 88]. Based on the reported data, the low-stimulation arms in each of these trials contain patients that could fall within this therapeutic range (see Table 3). Consequently, any residual benefit of 'low-stimulation' may have resulted in the overestimation of the efficacy of ASMs in the low-stimulation group.

This study has highlighted areas of focus for future research. There is a need for comparative studies assessing the long-term efficacy and safety of VNS Therapy as an adjunct to ASMs compared with relevant comparators. In addition, more research is required to reinforce the positive results observed for ASM load when VNS Therapy is used as an adjunct to ASMs.

Conclusions

Although there is much literature devoted to VNS Therapy, there is a paucity of comparative data and this should be a focus for future research. This meta-analysis demonstrated the benefits of VNS Therapy in people with DRE, which included improvement in seizure frequency without an increase in the rate of SAEs or discontinuations. The evidence validates the consideration of VNS Therapy for people

who are not responding to ASMs, or those who are unsuitable for or unwilling to undergo cranial procedures.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-022-10967-6.

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Author contributions FB, JM and VD conceptualised the project. SB and SM planned and conducted the investigation and the formal analysis. All authors were involved in the writing, review and editing of the manuscript.

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Declarations

Conflicts of interest Rohit Shankar has received institutional and research support from LivaNova, UCB, Eisai, Veriton Pharma, Bial, Averelle and GW pharmaceuticals outside the submitted work. He was the author/lead of the Royal College of Psychiatrists reports CR203, CR206 and the National Step Together Report. He is also the medical lead of the freely available SUDEP and Seizure safety Checklist and EpSMon App. He is the developmental disabilities representative in the recent NICE revision/update of the epilepsies (2022), the NHS RightCare report (2020), the NHS England specialist commissioning report for epilepsy (2021) and the National Confidential Inquiry into epilepsy deaths (2021–22). Joan Conry has received research funding from LivaNova. Jane Boggs has received research funding from LivaNova, Medtronic and UCB. Francesca Barion, Joanna Murphy and Vanessa Danielson are employees of LivaNova. Sarah Batson, Stephen Mitchell and Rodney Radtke have no competing interests to declare that are relevant to the content of this article.

Ethical standards The manuscript does not contain clinical studies or patient data.

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Optimization of Transcutaneous Vagus Nerve Stimulation Using Functional MRI

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ABSTRACT

Objective/Hypothesis
Vagus nerve stimulation (VNS) is an established therapy for drug-resistant epilepsy, depression, and a number of other disorders. Transcutaneous stimulation of the auricular branch of the vagus nerve (tVNS) has been considered as a non-invasive alternative. Several functional magnetic resonance imaging (fMRI) studies on the effects of tVNS used different stimulation parameters and locations in the ear, which makes it difficult to determine the optimal tVNS methodology. The present study used fMRI to determine the most effective location for tVNS.

Materials and Methods
Four stimulation locations in the ear were compared: the inner tragus, inferoposterior wall of the ear canal, cymba conchae, and earlobe (sham). Thirty-seven healthy subjects underwent two 6-min tVNS stimulation runs per electrode location (monophasic rectangular 500 μs pulses, 25 Hz). General linear model was performed using SPM; region-of-interest analyses were performed for the brainstem areas.

Results
Stimulation at the ear canal resulted in the weakest activation of the nucleus of solitary tract (NTS), the recipient of most afferent vagal projections, and of the locus coeruleus (LC), a brainstem nucleus that receives direct input from the NTS. Stimulation of the inner tragus and cymba conchae activated these two nuclei as compared to sham. However, ROI analysis showed that only stimulation of the cymba conchae produced a significantly stronger activation in both the NTS and LC than did the sham stimulation.

Conclusions
These findings suggest that tVNS at the cymba conchae properly activates the vagal pathway and results in its strongest activation, and thus may be the optimal location for tVNS therapies applied to the auricle.

https://www.neuromodulationjournal.org/article/S1094-7159(21)03491-7/fulltext

Transcutaneous auricular vagus nerve stimulation.

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SUMMARY

Invasive vagus nerve stimulation (VNS) is an approved treatment for drug-resistant epilepsy. Besides recognized clinical efficacy in about 60% of patients, there are major drawbacks such as invasiveness and common side effects including hoarseness, sore throat, shortness of breath, and coughing. Invasive VNS applies electrical stimulation to the left cervical branch of the vagus nerve and excites thick-myelinated afferent nerve fibers. Peripheral vagus nerve afferent volley initiates brainstem activity in the nucleus of the solitary tract and provokes typical brainstem and cerebral activation patterns that mediate the anticonvulsive mode of action. Whereas invasive VNS is an established neuromodulatory treatment in drug-resistant epilepsy, transcutaneous VNS (tVNS) of the auricular branch of the vagus nerve is suggested to be an alternative access path to the same neuronal network without invasiveness. Preclinical and clinical studies indicate that especially the cymba conchae of the auricle is selectively supplied by the auricular branch of the vagus nerve. Recent anatomical data demonstrate existence and quantity of thick-myelinated afferent nerve fibers of the left auricular branch of the vagus nerve that carries 21% of thick-myelinated afferent nerve fibers counted in the left thoracic vagus nerve in humans. Projection of auricular branch of the vagus nerve afferents from the auricle to the nucleus of the solitary tract is known from histochemical and electrophysiological experiments in rodents and confirmed in humans by functional imaging. Cerebral activation patterns triggered by invasive and tVNS resemble each other in appearance. Clinical trials in patients address safety and performance of tVNS and provide evidence for application in drug-resistant epilepsy.

https://journals.lww.com/clinicalneurophys/Abstract/2019/11000/Transcutaneous_Auricular_Vagus_Nerve_Stimulation.7.aspx