Clinical Benefit of Vagus Nerve Stimulation for Epilepsy: Assessment of Randomized Controlled Trials and Prospective Non-Randomized Studies

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ABSTRACT

We examined the efficacy of vagal nerve stimulation (VNS) for patients suffering from medically intractable epilepsy. Four randomized controlled trials (RCTs - 3 adult RCTs and 1 pediatric RCT) were identified in our comprehensive literature search. Across the 4 studies, high frequency VNS stimulation (frequency >20 Hz) consistently achieved a greater seizure frequency reduction (23.4-33.1%) relative to low frequency VNS stimulation (1 Hz, .6-15.2%). We identified 2 RCTs examining whether the parameters of stimulation influenced seizure control. These studies reported that VNS achieved seizure control comparable to those reported by the first 4 RCTs (22-43% seizure frequency reduction), irrespective of the parameters utilized for VNS stimulation. In terms of VNS associated morbidity, these morbidities were consistently higher in adults who underwent high frequency VNS stimulation (eg dysphonia 37-66%, dyspnea 6-25.3%). However, no such differences were observed in the pediatric population. Moreover, <2% of patients withdrew from the RCTs/prospective studies due to intolerable symptoms. To provide an assessment of how the risks and benefits of VNS impact the patient experience, 1 study assessed the well-being of enrolled patients (as a secondary end point) and found VNS was associated with an overall improvement in well-being. Consistent with this observation, we identified a prospective, non-randomized study that demonstrated improved quality of life for epilepsy patients managed with VNS and best medical practice relative to best medical practice alone. In aggregate, these RCT studies support the efficacy and benefit of VNS as a neuro-modulatory platform in the management of a subset of medically refractory epilepsy patients.

KEYWORDS: epilepsy surgery, neuromodulation for epilepsy, vagus nerve stimulation, VNS for epilepsy, medically intractable epilepsy

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Introduction

Worldwide, an estimated 65 million people are afflicted with epilepsy making it the most common chronic neurological disease.[1,2] Furthermore, the costs associated with epilepsy care total ~$15.5 billion annually in the United States[3] and are further amplified by the toll of productivity loss associated with absences from work and school.[4] In addition to the economic burden, epilepsy patients are faced with seizure associated injuries and premature mortality.[1,5,6] Recurrent seizures and the associated depression/anxiety imparts epilepsy patients with a reduced quality of life.[7-9] Therefore, there remains an unmet need for curative or seizure-suppressive therapies for epilepsy patients.

Antiepileptic seizure medications (ASMs) are the first-line therapy for epilepsy. Despite the availability of many ASMs, ~36% of patients suffer from medically intractable seizures (ie, ongoing seizures despite the use of 2 or more ASMs).[10] In these patients, seizure control with the addition of a third ASM is likely to occur in only 13% of patients.[11] Surgical treatment is a therapeutic consideration for patients that fail to achieve adequate seizure control with medical management. For example, localization and resection of epileptogenic foci can lead to dramatic reductions in seizure frequency.[12] The most established form of epilepsy surgery involves mesial temporal lobe resection[13] where several landmark RCTs have demonstrated notable improvement in seizure frequency and improvement of quality of life in affected patients,[14,15] including children.[16]

Despite the success of resective surgery for some forms of epilepsy, there is a large population of patients with medically intractable epilepsy who have either failed resective epilepsy surgery[17,18] or who are not candidates for resective surgery.[19] For those patients, neuromodulation therapies including responsive neurostimulation,[20] deep brain stimulation[21] or vagal nerve stimulation (VNS)[22] have emerged as therapeutic options to reduce the seizure burden. VNS was approved by the United States Food and Drug Administration in 1997 and

subsequently has been adopted in more than 70 countries for a wide array of medically intractable seizures including localization-related epilepsy (with multiple or unresectable foci), after unsuccessful intracranial epilepsy operations, and in generalized epilepsy syndromes.[23]

Here we review pertinent RCTs that have examined VNS as an adjunctive therapy for medically intractable epilepsy.

Methods

The scientific literature cataloged in the PubMed (MEDLINE) electronic database (https://www.ncbi.nlm.nih.gov/pubmed/) was searched between 1980-2020 (cutoff date January 1, 2020) using the following terms: vagal nerve stimulation epilepsy or vagus nerve stimulation epilepsy. Inclusion criteria for the initial search were set by the following restrictions: (1) original research defined by a 'comparative study' or 'randomized controlled trial' study type, (2) published in the English language, and (3) involved human subjects. Using the search criteria, 129 articles were identified. Articles were screened and excluded on manual review if they did not include RCT data related to the efficacy of implanted vagus nerve stimulation (ie, transcutaneous VNS studies were excluded) for the treatment of medically refractory epilepsy as a primary or secondary outcome, enrolled <20 patients or focused investigation of VNS efficacy for syndromic epilepsy (eg, Lennox-Gastaut syndrome). Eighteen relevant articles reporting the findings from 7 different clinical trials were identified (see Table 1 for references to relevant articles associated with each trial). A secondary search of the Cochrane database failed to identify additional RCTs that were not found on the initial PubMed search. Paper components reported include: author, year of publication, years of data collection, number of study sites, study design, number of patients, patient inclusion and exclusion criteria, interventions utilized in the study groups, primary and secondary outcomes, main findings with an emphasis on those studying the reduction in seizure frequency, complication rates, and study limitations or sources of potential bias (see Table 1 for a summary of included studies).

The risk of bias across 7 domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete data, selective reporting, and other) was assessed for the primary published article from each of the 7 trials using The Cochrane collaboration's tool for assessing risk of bias in randomized trials.[24] The risk of bias was judged (high, low, or unclear) based on the Cochrane tool's criteria for each of the RCTs reviewed (see Table 2 for a risk of bias assessment summary).

Results

Efficacy of VNS for Medically Refractory Epilepsy

Three RCTs have assessed the efficacy of VNS for medically refractory epilepsy in patients ≥12 years old.[25-27] 1 RCT has examined the efficacy of surgery for drug-resistant epilepsy in children ages 4-14.[28]

The first RCT by Handforth et al enrolled 254 patients across 20 medical centers.[26] Following enrollment, baseline seizure frequency was established through a 12- to 16 week observation period. A stable regimen of 1-3 ASMs for ≥1 month or 5 half-lives plus 2 weeks (whichever was longer) was required before study entry. Patients 12-65 years old with ≥6 partial seizures (note, the inclusion criteria as originally stated for the trials is described here but the terminology has been revised to for simple partial seizures and complex partial seizures which are now termed focal aware and focal impaired awareness seizures, respectively) on this stable regimen over a 30 day period, with no more than 21 days between seizures underwent VNS implantation (NeuroCybernetic Prosthesis, Cyberonics, Inc, Webster, TX). Participants were then randomized to therapeutic (high) stimulation (n = 94) or minimally therapeutic (low) stimulation (n = 102). Exclusion criteria are outlined in Table 1.

Following enrollment, ASM regimens were not altered except to maintain appropriate serum concentrations or in response to toxicity. The study was divided into a baseline (12-16 weeks) and treatment phase which began 2 weeks after VNS implantation and lasted for 3 months. Patients were randomized to high (anticipated to be therapeutic) or low stimulation (anticipated to be subtherapeutic and thus the active control group) at the start of the treatment phase. The high stimulation parameters were on/off 30 s/5 min, 500 μs pulse width, 30 Hz frequency with titration of stimulus amplitude up to 3.5 mA as tolerated (average final current setting was 1.3 mA). Patients in the high stimulation group could also self-trigger an "on" period to attempt to abort an anticipated seizure. Low stimulation parameters consisted of on/off 30 s/3 hrs, 130 μs pulse width, 1 Hz frequency. Current was titrated to the perception threshold then held constant for the remainder of the trial (final average current setting was 1.2 mA).

The primary outcome was the between-groups (high vs low stimulation) percentage change in total seizure frequency during the treatment period compared to baseline. Seizure diaries (with or without the assistance of the patient's caregiver) were used to determine seizure frequency. Diaries included descriptions of seizures including seizure type and associated motor manifestations. Episodes without an observable motor component were not counted as seizures. Secondary outcome measures included between-group comparisons of seizures involving alteration of awareness, within-group changes in seizure frequency during treatment compared to baseline, and number of patients responding with 50% or 75% seizure-frequency reductions. Global evaluation scores of patient well-being (rated by the blinded interviewer, patient, and companion) were analyzed with both between groups and within-group comparisons. Adverse events (serum gastrin, Holter monitoring cardiac data, pulmonary function values, serum ASM levels, vital signs, and body weights) were analyzed for changes from baseline both between and within groups.

Table 1. Study Characteristics.

STUDY NAME, CITATION(S)* (YEAR)	(1) CENTERS; (2) # OF PATIENTS; (3) YEARS	(1) INCLUSION CRITERIA; (2) EXCLUSION CRITERIA	(1) INTERVENTION(S); (2) STIMULATION PARAMETERS; (3) BASELINE AND TREATMENT PHASE DURATION	(1) PRIMARY OUTCOME(S); (2) SECONDARY OUTCOMES	POST-INTERVENTION SEIZURE RATE AND CLINICAL OUTCOME
PuLsE, Ryvlin et al, (2014)[31]	(**1**) 28 centers (**2**) 131 (**3**) 2006-2008	(**1**) 16-75 years, ≥2 years of intractable focal seizures, failure of ≥3 ASMs, stable regimen ≥1 ASM for 1 month prior to enrollment, ≥1 focal seizure with a motor component per month during the 2 months prior to enrollment (**2**) psychogenic seizures or genetic (idiopathic) generalized epilepsies	(**1**) VNS + BMP or BMP (**2**) Variable during the study (**3**) Baseline: 8 weeks Intervention: 12 months	(**1**) Change in QOLIE-89 score (**2**) QOLIE-89 subscores, 50% responder rate[&], CES-D scores, NDDI-E scale, CGI-I scale, AEP, change in ASMs	No difference in 50% responder rate[&] between VNS + BMP vs BMP. Significant improvement in QOLIE-89 and CGI-I in VNS + BMP vs BMP. No difference in CES-D, NDDI-E, or ASM load. Significant reduction in seizures per week observed with VNS + BMP compared to BMP.
NA, klinkenberg et al, (2012)*[6,7,20,39] **Pediatric FDA approval**	(**1**) 1 center (**2**) 41 (**3**) not reported	(**1**) Intractable epilepsy, 4-14 years, ineligible for epilepsy surgery, informed consent (**2**) non-epileptic seizures, SE within 3 months, progressive cerebral lesion, degenerative disorder, or malignancy within 5 years, unstable disease within 2 years, schizophrenia or psychosis, high surgical risk, drug or alcohol abuse, or psychiatric disorder requiring electroconvulsive therapy or chronic use of tranquillizers within 6 months, antihistamine, metoclopramide, or CNS-active compounds, experimental drug in previous 30 days	(**1**) High or low output stimulation (**2**) High output: .25-1.75 mA, on/off 30 s/5 min, 30 hz, .5 m. low output: .25 mA, on/off 14 s/60 min,1 hz, .1 ms (**3**) Baseline: 12 weeks Intervention: 20 weeks	(**1**) 50% responder rate[&] (**2**) seizure severity (NHS3), adverse events, IQ	No significant difference in 50% responder rate[&] (high-output 16% vs low-output 21%) or seizure severity at 20 weeks. Adverse events were not compared between treatment groups and IQ outcome was not reported
NA, DeGiorgio et al, (2005)[29]	(**1**) "Multicenter" (specific number not erported) (**2**) 64 (**3**) not reported	(**1**) ≥12 years old, ≥1 ASM, ≥1 seizure/30 days with alteration of consciousness for 3 months prior to enrollment. Additional eligibility criteria following baseline: ≥1 seizure with loss or alteration of consciousness, no change in ASMs (**2**) active cardiac, pulmonary, or peptic ulcer disease, vagotomy, general anesthesia within 30 days, concomitant investigational drug or device, or unstable medical condition. Failure to meet additional inclusion criteria during the 4-week baseline period	(**1**) High, medium, or low duty cycle VNS stimulation (**2**) 3 modes of VNS A: 7 s/18 s (on/off), 28% (duty-cycle), .25-1.5 mA, 20 hz, 500 μ s. B: 30 s/30 s, 50%, .25-1.5 mA, 20 hz, 250 μ s C: 30 s/3 min, 14%, .25-1.5 mA, 30 hz, 500 μ s. (**3**) baseline: 4 weeks. Intervention: 3 months	(**1**) Percentage change in seizure frequency (**2**) none	50% responder rate[&] was 31.6%, 31.7% and 26.1%, respectively for groups A (n = 19), B (n = 19), and C (n = 23) (no significant difference between groups). The median reduction in seizure frequency was 22%, 26%, and 29%, respectively for groups A, B, and C (no significant difference between groups)
EO5, handforth et al (1998)*[26,40,41] **Initial FDA approval study**	(**1**) 20 centers (**2**) 254 (**3**) 1995-1996	(**1**)12-65 years, ≥6 partial-onset seizures involving alterations in consciousness over 30 days with ≤21 days between seizures, female contraception use, stable on one of 3 ASMs for ≥1 month or 5 half-lives plus 2 weeks (whichever was longer) prior to study entry (**2**) deteriorating neurologic or medical conditions, pregnancy, cardiac or pulmonary disease, active peptic ulcer, nonepileptic seizures, ≥1 episode of SE in previous 12 months, prior vagotomy, inability to consent, prior VNS, prior brain stimulation, prior resective epilepsy surgery, or inability to perform pulmonary function tests or comply with clinic visits	(**1**) High or low stimulation (**2**) High stimulation: On/off 30 s/5 min, 500 μ s, 30 hz, up to 3.5 mA Low stimulation: On/off 30 s/3 hrs, 130 μ s, 1 Hz current increased to perception and held constant. (**3**) baseline: 12-16 weeks Intervention: 3 months	(**1**) Change in total seizure frequency (**2**) between-group comparisons of seizures involving alterations of awareness, within-group changes in seizure frequency, 50% responder rate[&], 75% responder rate[$], global well-being scores	Significantly greater (27.9%) reduction in mean seizure frequency and partial-onset seizures with alterations of awareness with high stimulation (n = 94) compared to 15.2% reduction with low stimulation (n = 102). Significantly greater 75% responder rate[$] (n = 10) with high stimulation vs low stimulation (n = 2). No difference in 50% responder rate[&] between high (n = 22) vs low (n = 16) stimulation. High stimulation group scored significantly better in global evaluations of well-being

(Continued)

Table 1. Continued.

STUDY NAME, CITATION(S)* (YEAR)	(1) CENTERS; (2) # OF PATIENTS; (3) YEARS	(1) INCLUSION CRITERIA; (2) EXCLUSION CRITERIA	(1) INTERVENTION(S); (2) STIMULATION PARAMETERS; (3) BASELINE AND TREATMENT PHASE DURATION	(1) PRIMARY OUTCOME(S); (2) SECONDARY OUTCOMES	POST-INTERVENTION SEIZURE RATE AND CLINICAL OUTCOME
NA, Scherrmann et al, (2001)[30]	(**1**) 1 centers (**2**) 28 (**3**) 1998-2001	(**1**) Medically intractable epilepsy, ≥4 complex-partial or generalized seizures per month (**2**) NR	(**1**) Standard or rapid cycle stimulation. (**2**) standard cycle stimulation: On/off 30 s/300 s, 500 μ s, 30 hz, .25-3.0 mA. Rapid cycle stimulation: On/off 7 s/30 s, 250 μ s, 20 hz, .25-3.0 mA. (**3**) baseline: NR. Intervention: NR	(**1**) 50% responder rate[&] (**2**) Subjective evaluation of seizure frequency, severity, postictal recovery, duration of seizure-free intervals, and health-related QOL	No difference in 50% responder rate[&] between rapid cycle (36%, n = 5) vs standard (43%, n = 6) stimulation. Secondary outcomes NR for the subgroup of patients that underwent the randomized trial
EO3, VNS group (1995), Elger et al, (2000)*[25,42–47] **Initial FDA approval study, pediatric approval**	(**1**) 17 centers (**2**) 125 (**3**) not reported	(**1**) Intractable epilepsy with ≥6 seizures per month, predominately partial seizure types (simple, complex, or secondarily generalized) based on ILAE classification, ≥12 years of age. (**2**) progressive or unstable neurologic illness other than epilepsy, any unstable medical condition, pregnancy, use of >3 or investigational ASMs at study entry	(**1**) High or low stimulation (**2**) High stimulation: On/off 30-90 s/5-10 min, 500 μ s, 20-50 hz, .25-3.0 mA. Low stimulation: On/off 30 s/60-180 min, 130 μ s, 1-2 hz, .25-2.75 mA. (**3**) baseline: 12 weeks. Intervention: 14 weeks (final 12 weeks used for analysis)	(**1**) Percentage change in total seizure frequency compared to baseline (**2**) absolute difference in seizure frequency compared to baseline, 50% responder rate[&]	Significantly greater (24.5%, n = 54) reduction seizure frequency and 50% responder rate[&] (n = 17) with high stimulation compared to 6.1% (n = 60) reduction and n = 8 achieving 50% reduction in seizures with low stimulation. Significant decrease in seizure number for the high stimulation group and no change in the low stimulation group
NA, Michael et al, (1993)[27]	(**1**) 3 centers (**2**) 22 (**3**) not reported	(**1**) Not reported (**2**) not reported	(**1**) High or low stimulation (**2**) High stimulation: On/off 30 s/5 min, 500 μ s, 30 Hz,1.0-3.0 mA. Low stimulation: On/off 30 s/60-90 min, 130 μ s, 1 hz, .25-.5 mA. (**3**) baseline: 12 weeks. Intervention: 14 weeks	(**1**) Percentage change in total seizure frequency compared to baseline (**2**)	Significantly greater (33.1%) reduction in mean seizure frequency with high stimulation (n = 10) compared to .6% reduction with low stimulation (n = 12) at 14 weeks

Abbreviations: ASM, anti-seizure medication; AEP, adverse event profile; AMTR, anteromesial temporal resection; BMP, best medical practice; CES-D, Centre for Epidemiologic studies depression scale; CGI-I, clinical global Impression of improvement scale; CNS, central nervous system; DR, drug resistant; EEG, electroencephalogram; HSSS, hague seizure severity scale; ILAE, International League Against epilepsy; IQ, intelligence quotient; MRI, magnetic resonance imaging; MTLE, mesial temporal lobe epilepsy; NDDI-E, neurological Disorders depression inventory in epilepsy scale; NHS3, adapted Chalfont seizure severity scale; NR, not reported; QOL, quality of life; QOLIE-89, quality of life in epilepsy inventory; SAH, selective amygdalohippocampectomy; SE, status epilepticus VNS, vagal nerve stimulator; VSMS, Vineland Social Maturity Scale.*Indicates major citation for the study[&]Proportion of patients with >50% decrease in seizure frequency compared to baseline[$]Proportion of patients with >75% decrease in seizure frequency compared to baseline

The treatment groups were balanced in all key demographic and clinical characteristics including baseline seizure frequency. Of the 254 patients enrolled in the study, 55 patients were discontinued from the baseline period and 1 patient was implanted but not randomized due to device-related infection. In total, 198 patients were randomized, and 1 patient was excluded due to inadequate seizure recording and 1 withdrew due to adverse symptoms, therefore 98.8% of patients completed the study.

Patients receiving high stimulation (n = 94) achieved a 27.9% mean decrease in seizure frequency while those receiving low stimulation (n = 102) experienced a 15.2% decrease compared to baseline (significant difference between groups, P = .02). In terms of secondary outcomes, the high stimulation group had a significantly greater reduction of partial-onset seizures with alteration of awareness than the low stimulation group (P = .02). The high stimulation group had an improved 75% responder rate (proportion of patients with ≥75% decrease in seizure frequency compared to baseline; n = 10) compared with the low stimulation (n = 2) group (P = .015). There was no difference in the 50% responder rate (proportion of patients with ≥50% decrease in seizure frequency compared to baseline) between high (n = 22) vs low (n = 16) stimulation (P = .172). There were no treatment related changes in serum chemistry, hematology, urinalysis, weight, vital signs, serum gastrin, cardiac rhythm or rate, or pulmonary function.

The within group analysis showed that both the high stimulation and low stimulation group achieved a significant reduction in both total seizure frequency and partial-onset seizures involving alterations of awareness compared to baseline. Finally, the high stimulation group scored significantly better than the low stimulation group in global evaluations of well-being (P < .001). In accordance with the study protocol, ASM therapy did not differ between or within groups compared to baseline.

Surgery-related complications included 2 patients with left vocal cord paralysis, 2 patients with facial paresis and fluid accumulation over the generator requiring drainage in 1 patient. Device related infections occurred in 3 patients. Most frequent adverse events included cough (42.7, 45.3%, low and high, respectively) and paresthesias (25.2, 17.9%, low and high, respectively) which occurred in both treatment groups significantly more frequently compared to baseline. The high stimulation patients were significantly more likely to experience

voice alterations (66.3%) and dyspnea (25.3%) compared to the low stimulation patients. Overall, the symptoms were rated as mild to moderate and did not require stimulation reduction. Two of the 196 patients implanted with VNS (1%) were discontinued from the trial due to adverse events.

The quality of this study was assessed using the Cochrane risk of bias tool[24] (Table 2). Because subjects can potentially infer their stimulation parameters based on new onset symptoms after VNS placement, there is risk for performance bias. Because the global assessment of well-being is done by a blinded reviewer, performance bias is minimized, though not eliminated in this assessment. Furthermore, since seizure frequency is self-reported, there is also risk for detection bias. Finally, the study was sponsored by the manufacturer of the device being studied.

The second RCT by George et al[25] evaluated the efficacy of VNS at 17 centers and enrolled 125 patients of which 114 proceeded to VNS implantation and randomization in combination with ASM therapy (Table 1). Inclusion criteria consisted of patients ≥12 years old with medically intractable seizures, defined as a frequency of ≥6 per month and predominantly partial seizure types (simple, complex, or secondarily generalized) according to the International League Against Epilepsy classification. Exclusion criteria included: (1) progressive or unstable neurologic illness other than epilepsy, (2) any unstable medical condition, (3) use of >3 ASMs at the time of study entry, (4) pregnancy, and (5) use of an investigational ASM.

A 12 week baseline assessment was performed during which seizure frequency, type and duration as well as other baseline information including serum ASM concentrations was recorded. After the baseline, patients with <6 seizures per month, any seizure-free interval >14 days or ≥20% variation in any ASM level were excluded. After completion of the baseline, eligible patients underwent VNS implantation (NeuroCybernetic Prosthesis, Cyberonics, Inc, Webster, TX) and, following a 2 week recovery period, patients were randomized to receive either high or low stimulation for 14 weeks (the final 12 weeks was used for the subsequent efficacy analysis). The treatment stimulation parameters are described in Table 1. The self-activation mode was disabled in the low stimulation group (though the patients were not informed of this).

The primary outcome variable was the percent difference in overall seizure frequency compared to baseline. Secondary outcomes included the absolute difference in seizure frequency between the baseline and stimulation as well as the 50% responder rate in each group.

The 2 arms of the study were balanced in all key demographic and clinical characteristics with no significant differences between the groups including baseline seizure frequency. Of the 125 patients enrolled in the study, 11 patients were discontinued from baseline (due to failing protocol eligibility). Therefore, 114 patients were randomized to the high stimulation or low stimulation group.

Patients receiving high stimulation (n = 54) achieved a 24.5% mean decrease in total seizure frequency compared to patients receiving low stimulation (n = 60) which demonstrated a 6.1% decrease compared to baseline, which was significantly different between groups (P = .01). The secondary outcomes demonstrated that the high stimulation group achieved a significantly greater reduction in seizure frequency compared to baseline (P < .01) whereas patients receiving low stimulation did not (P = .21). Of the high stimulation group, 31% (n = 17) were 50% responders vs 13% (n = 8) of the low stimulation group (P = .002).

Surgery-related complications included 2 signal generator malfunctions requiring device explant. One patient in the high stimulation group (without a history of cardiac disease) had a nonfatal myocardial infarction, therefore, the generator was deactivated and explanted. Adverse events included hoarseness/voice changes (37.2, 13.3%, high and low stimulation, respectively) which were significantly more common in the high stimulation group (P < .01). Other adverse events (not significantly different between groups) included throat pain (11.1%), coughing (7.4%), dyspnea (5.6%), paresthesia (5.6%), muscle pain (5.6%), and headache.

We assessed the quality of this study using the Cochrane risk of bias tool (Table 2).[24] The risk of attrition bias is highlighted by the 24 patients who had major protocol violations including stimulation outside of the study range. Though a separate analysis was performed excluding these patients, it is unclear how this affected the outcome based on an intention-to-treat model. Finally, the study was sponsored by the manufacturer of the device being studied.

A third RCT by Michael et al,[27] evaluated the efficacy of VNS as an adjunctive therapy in 22 patients with medically refractory partial seizures across 3 centers. Patients who proceeded to VNS placement were randomized to either high stimulation (treatment) or low stimulation (control) with continued, stable ASM therapy. Inclusion and exclusion criteria were not specifically described in the publication.

A 12 week baseline assessment established ASM serum levels, psychosocial survey data, vital signs and seizures rates. Patients then underwent VNS placement (NeuroCybernetic Prosthesis, Cyberonics, Inc, Webster, TX) and (following a 2 week recovery period) were randomized to receive either high or low stimulation (parameters are indicated in Table 1) for 14 weeks (the final 12 weeks was used for the subsequent efficacy analysis).

The primary outcome variable was the percent difference in overall seizure frequency compared to baseline. It is unclear if the 2 arms of the study were balanced in terms of demographic and clinical characteristics. Few patient characteristics were reported and those that were referred to the entire study population (not subgroups).

The high stimulation group (n = 10) achieved a 33.1% mean decrease in seizure frequency compared to baseline (P = .0084) while patients receiving low stimulation (n = 12) experienced a non-significant .6% decrease compared to baseline (P = .9183). Overall, there was a significant difference in the reduction of seizure

frequency between the high- and low stimulation groups (32.5%, P = .0115). Of the high stimulation group, 30% (n = 3) were 50% responders vs 0% (n = 0) of the low stimulation group (no between-group statistical analysis was reported for this measure).

No deaths or serious injury related to surgery were reported. All patients completed the study. Adverse events (reported only during stimulation) included hoarseness/voice changes (40%, 42%, low and high, respectively), nausea (30%, 0%, low and high, respectively), and coughing (40%, 17%, low and high, respectively).

The quality of this study was assessed using the Cochrane risk of bias tool (Table 2).[24] The risk of selection bias is unclear because demographic characteristics were not reported for the 2 study groups. There is a risk of performance bias in the study because though both treatment and control arms underwent surgery and received VNS, the on/off cycles (which are readily perceived by the patients) differed drastically between groups and there was no information reported regarding the blinding procedure. The risk of attrition bias is low as there was limited attrition of those enrolled in the study following randomization and all of the patients excluded from the outcome analysis were accounted for. Finally, the study was sponsored by the manufacturer of the device being studied.

Efficacy of VNS for Medically Refractory Epilepsy in Children

One RCT examined the efficacy of VNS for medically refractory epilepsy in pediatric patients.[28] The single center study enrolled 41 subjects who proceeded to VNS placement and were randomized to either high stimulation (treatment) or low stimulation (control) concurrent with continued, stable ASM therapy. Inclusion criteria consisted of patients 4 - 18 years old with medically intractable epilepsy not eligible for epilepsy surgery from whom informed consent was obtained from parents or guardians. Exclusion criteria are indicated in Table 1.

Patients underwent a 12 week baseline assessment during which seizure frequency, type (International League Against Epilepsy classification), duration and severity (estimated using the adapted Chalfont Seizure Severity Scale, NHS3) as well as IQ (assess using the Peabody Picture Vocabulary test and Beery-Buktenica Developmental Test of Visual-Motor Integration, fifth edition) and mean number of ASMs were recorded.

After completion of the baseline, 41 patients underwent VNS placement (NeuroCybernetic Prosthesis, Cyberonics, Inc, Webster, TX). Following a 2 week recovery period, patients were randomized to either high- or low stimulation treatment (parameters are indicated in Table 1) for 20 weeks.

The primary outcome variable was the percent difference in overall seizure frequency compared to baseline. Secondary outcomes included seizure severity, overall satisfaction, adverse events and IQ.

The 2 arms of the study were balanced in all key demographic and clinical characteristics with no significant differences between the groups including baseline seizure frequency. Of the 41 patients enrolled in the study, 3 patients were discontinued (2 from the high stimulation group and 1 from the low stimulation group) due to unreliable/incomplete seizure diaries. Therefore, 38 completed the study period and were included in the outcome analyses.

In terms of the primary endpoint, patients receiving high stimulation (n = 19) achieved a 23.4% median decrease in total seizure frequency compared to patients receiving low stimulation (n = 19) which demonstrated an 8.8% median decrease compared to baseline. The between-group effect on seizure frequency was not different (P = .61). Of the high stimulation group, 16% (n = 3) were 50% responders vs 21% (n = 4) of the low stimulation group (P = 1.00). The secondary outcomes demonstrated no difference in seizure severity between the high and low stimulation groups and the effect on IQ outcome was not reported.

Surgery-related complications included 2 wound infections that were treated with antibiotics and did not require device explant. Adverse events included hoarseness/voice changes, throat pain, coughing, dyspnea, paresthesia, muscle pain, and headache. Adverse event frequency was not statistically compared between groups.

Study quality was assessed using the Cochrane risk of bias tool (Table 2).[24] There is a high risk of selective reporting of outcome data because IQ was stated as an outcome measure but was not reported. The risk of attrition bias is low as there was limited attrition of those enrolled in the study following randomization and all of the patients excluded from the outcome analysis were accounted for. Finally, the study was sponsored by the manufacturer of the device being studied.

VNS Stimulation Parameters and Seizure Control: Randomized Controlled Trials

Two non-blinded RCTs compared the efficacy of different stimulation parameters for reducing medically intractable seizures.

DeGiorgio et al investigated the optimal range of VNS stimulation in terms of duty cycle for intractable epilepsy.[29] Multiple centers enrolled 64 patients and evaluated the efficacy of 3 different VNS stimulation paradigms in combination with continued, stable ASM therapy. The inclusion criteria consisted of patients ≥12 years old with ≥1 ASM, and ≥1 seizure inducing alteration of consciousness per 30 days. Exclusion criteria included: (1) active cardiac, pulmonary, or peptic ulcer disease, (2) vagotomy, (3) general anesthesia within 30 days, (4) concomitant investigational drug or device, 5) unstable medical condition, or (6) subjects who could not document ≥1 seizures with loss of consciousness per 30 days for the 3 months prior to enrollment.

Subjects underwent a 4 week baseline assessment during which seizure frequency, type and duration as well as

Table 2. Risk of Bias Assessment.

STUDY AUTHORS (YEAR)	RANDOM SEQUENCE GENERATION (SELECTION BIAS)	ALLOCATION CONCEALMENT (SELECTION BIAS)	BLINDING OF PARTICIPANTS AND PERSONNEL (PERFORMANCE BIAS)	BLINDING OF OUTCOME ASSESSMENT (DETECTION BIAS)	INCOMPLETE OUTCOME DATA (ATTRITION BIAS)	SELECTIVE REPORTING (REPORTING BIAS)	OTHER BIAS
Ryvlin et al (2014)[31]	Low	High	High	High	High	High	Unclear
Klinkenberg et al (2012) [28]	Low	Low	Unclear	Unclear	Low	High	Unclear
DeGiorgio et al (2005) [29]	Low	Unclear	High	High	Low	Low	Low
Handforth et al (1998) [26]	Low	Low	Unclear	Unclear	Low	Low	Unclear
Scherrmann et al, (2001) [30]	Unclear	High	High	High	Low	High	Low
VNS group et al (1995) [25]	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Michael et al (1993)[27]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear

information including ASM regimen was recorded. Upon completion of the baseline period, patients meeting the additional eligibility criteria: ≥1 seizure involving a loss or alteration of consciousness and no change in ASMs since enrollment underwent VNS implantation (NeuroCybernetic Prosthesis, Cyberonics, Inc, Webster, TX). A total of 64 patients were initially randomized to receive 1 of 3 different VNS stimulation programs for a 3-month trial period. Group A stimulation parameters were: on/off 7 s/18 s, duty-cycle 28%, 500 μs pulse width, 20 Hz frequency, .25-1.5 mA (titrated to the highest amplitude tolerated); Group B stimulation parameters were: on/off 30 s/30 s, duty-cycle 50%, 250 μs pulse width, 20 Hz frequency, .25- 1.5 mA (titrated to the highest amplitude tolerated); and Group C stimulation parameters were: on/off 30 s/3 min, duty-cycle 14%, 500 μs pulse width, 30 Hz frequency, .25- 1.5 mA (titrated to the highest amplitude tolerated).

The primary outcome variables were within-group and between-group percentage differences in seizure frequencies. Of the 64 patients enrolled, one patient developed a device infection requiring explant, 1 patient could not tolerate stimulation and was converted to standard VNS stimulation (excluded from the study) and 1 patient was lost to follow-up. Therefore, 61 patients completed the trial period across Group A (n = 19), Group B (n = 19), and Group C (n = 23). Demographic characteristics of the 3 groups were not reported. The final output current at completion of the study was not different between groups.

In terms of the primary endpoint, patients in all 3 groups achieved a significant reduction in cumulative seizure frequency. The median reduction in seizure frequency was 22% (n = 4) for Group A ($P = .0078$), 26% (n = 5) for Group B ($P = .0270$), and 29% (n = 7) for Group C ($P = .0004$). There was no between-group difference in seizure frequency, 50% responder rate or 75% responder rate.

One patient developed an infection requiring explant of the device and 1 patient could not tolerate the test stimulation necessitating conversion to standard VNS stimulation (the patient was therefore excluded from the study analysis). Adverse events across groups included pain at the electrodes or generator (n = 13), throat pain/pharyngitis (n = 6), cough (n = 6) and voice changes (n = 3). Cough and voice alteration were more common among group A (26% compared to 5% group B and 9% for group C).

The quality of the study was assessed using the Cochrane risk of bias tool (Table 2).[24] There is a risk of selection bias due to allocation concealment as the procedure for concealment is not described. There is a risk of selective reporting as outcome data were evaluated and reported in full for all participants in the trial. The risk of bias from other sources appears to be low as there does not appear to be any other sources of bias and the study was not sponsored by the device manufacturer.

Scherrmann et al compared the efficacy of rapid cycle to "standard" VNS stimulation for intractable epilepsy.[30] The study enrolled 28 patients at a single center and evaluated the efficacy of 2 different VNS stimulation paradigms in combination with continued ASM therapy. Inclusion criteria consisted of patients with medically intractable epilepsy, and ≥4 complex-partial or generalized seizures per month. No exclusion criteria were reported.

Patients meeting selection criteria underwent a baseline assessment (duration not reported) to record seizure frequency, type and duration as well as the ASM regimen. Patients then underwent VNS placement (NeuroCybernetic Prosthesis, Cyberonics, Inc, Webster, TX). A total of 28 patients were randomized to receive either standard (on/off 30 s/300 s, 500 μs pulse width, 30 Hz frequency) or rapid cycle (on/off 7 s/30 s, 250 μs pulse width, 20 Hz frequency) VNS stimulation. In both stimulation groups, the pulse amplitude was titrated from .25 up to 3.0 mA (as tolerated).

The primary outcome was between-group differences in 50% responder rate. Twenty-eight patients were randomized between standard stimulation (n = 14) and rapid cycle stimulation (n = 14). Demographic characteristics of the 28 patients that underwent the embedded randomized controlled trial of VNS stimulation programs were not reported.

In terms of the primary endpoint, there was no difference in the 50% responder rate for patients receiving standard stimulation 43% (n = 6) and those receiving rapid cycle stimulation 36% (n = 5; $P = .70$). The median reduction in seizure frequency was not reported for the subgroup of patients who underwent the embedded randomized controlled trial.

The quality of this study was assessed using the Cochrane risk of bias tool (Table 2).[24] There is a high risk of selection bias due to allocation concealment because the allocation was not blinded to subjects or study personnel. There is a high risk of selective reporting as outcome data appear to be reported in full for participants in the randomized controlled portion of the trial, however, there is insufficient information reported to determine this definitively. Furthermore, the study was nonblinded so both subjects and study personnel were aware of which group individuals were assigned. There is a high risk of selective reporting bias as the seizure frequency for the 2 treatment groups as well as the secondary outcome measures were not reported specifically for the subjects that participated in the randomized controlled component of the trial but rather for the entire study population. Other risk of bias is low as there does not appear to be any other sources of bias and the study was not sponsored by the device manufacturer.

VNS and best medical practice vs best medical practice on seizure frequency: Non-randomized prospective study

Ryvlin et al examined the efficacy of VNS in combination with best medical practice (BMP) ASM administration vs BMP alone for medically intractable epilepsy.[31] The study was conducted at 28 centers and enrolled 131 patients of whom 122 proceeded to randomization to either VNS plus BMP or BMP alone. Inclusion criteria consisted of patients 16-75 years old with ≥ 2 year history of medically intractable focal seizures, previous failure of ≥3 ASMs (alone or in combination), treatment with ≥1 ASM (on a stable regimen for ≥1 month prior to study entry), and ≥1 focal seizure (with a motor component) per month during the 2 months prior to study entry. Exclusion criteria included: (1) psychogenic nonepileptic seizures or, (2) genetic (idiopathic) generalized epilepsies.

Selected patients underwent an 8 week baseline assessment to record seizure frequency and other health outcomes. Patients were then randomized to either VNS + BMP or BMP. Those randomized to the VNS + BMP group underwent VNS placement (NeuroCybernetic Prosthesis, Cyberonics, Inc, Webster, TX) a median of 48 days (range 8-162 days) following randomization. VNS stimulation parameters varied throughout the study and on a patient-by-patient basis.

The primary outcome was mean change from baseline in the 89-item Quality of Life in Epilepsy Inventory (QOLIE-89) total score. Secondary outcomes included QOLIE-89 composite subscores, 50% responder rate, scores on the Center for Epidemiologic Studies Depression scale (CES-D), Neurological Disorders Depression Inventory in Epilepsy scale (CGI-I), Adverse Event Profile (AEP), and change from baseline in ASM load. Safety and tolerability were also evaluated based on adverse event reporting and premature study withdrawals.

The 2 arms of the study were balanced in all key demographic and clinical characteristics with no significant differences between the groups including baseline seizure frequency, ASM load and mean baseline inventory scores (QOLIE-89, AEP, CES-D, NDDI-E, and CGI-I). Ten patients randomized at 1 study site were excluded due to incorrect consent form use. Therefore, 112 patients were included in the safety analysis and 96 patients (n = 48 in the VNS + BMP group and n = 48 in the BMP group) with adequate follow-up completion were ultimately included in the final analysis.

After 12 months of study intervention, patients receiving VNS + BMP (n = 48) achieved significantly greater improvements in QOLIE-89 and CGI-I compared to the BMP group (n = 48). There were no significant differences in QOLIE-89 subscales, CES-D, NDDI-E, AEP or ASM load between VNS + BMP compared to the BMP group. The decrease in total number of seizures per week was significantly greater in the VNS + BMP group compared to the BMP group ($P = .03$). The median percent change in seizure frequency from baseline to 12 months was not significantly different between the VNS + BMP group vs the BMP group. There was not a significant difference in the 50% responder rate between VNS + BMP and BMP groups.

A significantly greater number of patients (43%, n = 23) in the VNS + BMP group reported adverse events compared to 21% (n = 12) in the BMP group. Specific adverse events in the VNS + BMP group (not reported in the BMP group) included

dysphonia (n = 8, 15%), chest pain (n = 3, 6%), headache (n = 3, 6%), hypoesthesia (n = 3, 6%), depression (n = 3, 6%), transient vocal cord paralysis (n = 2, 4%) and brief postoperative respiratory arrest from laryngospasm (n = 1, 2%) which resolved on the same day. One patient experienced an infection related to device implantation. No deaths were reported and no discontinuations due to an adverse event occurred in either treatment group.

The quality of this study was assessed using the Cochrane risk of bias tool.[24] There is a high risk of allocation concealment selection bias, performance bias, and detection bias as this was an open label trial and participants were therefore aware of their treatment allocation. There is a high risk of bias due to incomplete outcome data as there is insufficient information to determine which groups were affected by incomplete outcome data reported in the trial and due to low trial enrollment. Furthermore, there was a post-hoc change in statistical methods used for the outcome analysis which violates the intention-to-treat trial design. There is a high risk of selective reporting bias as there is insufficient information to determine which groups were affected by incomplete outcome data reported in the trial. Another risk of potential bias includes the sponsorship by the manufacturer of the device studied (Table 2).

Discussion

Our review of the RCTs and prospective non-randomized studies suggests that VNS offer palliative benefit for patients whose epilepsy is refractory to medical management and is not amenable to resective surgery. Across 6 RCTs, high frequency VNS (>20 Hz) achieved a higher seizure frequency reduction (22-43%) relative to low frequency VNS stimulation (1 Hz, .6-15.2%) or to baseline seizure frequency. While the reduction in seizure frequency did not reach significance in every RCT, the studies that reported insignificant differences were also those with fewer patients, suggesting that inadequate sample size contributed to the variation in the reported outcome. Morbidities associated with VNS include hoarseness (15-66%), cough (7-45%), pain (11%), dyspnea (6 - 25%), paresthesias (7.9%) and nausea (30%).[25-27,29,31] The quality-of-life and global well-being assessments by Ryvlin et al and Handforth et al suggest that the benefits of seizure control generally outweigh the VNS associated morbidities.

Despite the demonstrated benefit of VNS for medically intractable epilepsy, not all patients improve with this therapy. Approximately 25% of those receiving VNS therapy do not ultimately achieve a therapeutic benefit and <5% of patients attain complete freedom from seizures.[32] Therefore, the efficacy of VNS as a means of seizure control is far from universal. Biomarkers that allow identification of seizure patients who would most likely benefit from VNS would be of great value in the clinical management of epilepsy. Individuals may receive little or no benefit from VNS and this must be communicated during treatment discussions with patients. Another consideration when interpreting the data reported in the RCTs included in the review is that 5 of the 7 studies were supported by the VNS manufacturer, Cyberonics, Inc.[25-28,31]

In aggregate, the effect size in seizure frequency reduction reported by the RCTs was significantly lower relative to that reported by a meta-analysis of 3321 patients from 77 reports (including observational studies). In this meta-analysis, VNS reduced seizure frequency by ≥ 50% in ~50% of patients, with a delayed benefit >1 year after device implantation.[25-27,32] An unblinded review of the device manufacturer's patient outcome database yielded a similar reduction in seizure frequency. For example, ≥50% reduction in seizure frequency occurred in 1972 of 4483 (44%) within 3 months of VNS therapy and in 618 of 1104 (56%) patients after 24 months.[33] Finally, a review of a large Japanese VNS registry of 362 children and adults showed that the 50% responder rate improved from 55.8% at 1-year, to 57.7% at 2 years, and 58.8% at 3 years.[34] A possible explanation for the discrepancy in efficacy is that follow-up was limited to 3-5 months in the RCTs which limit the detection of delayed therapeutic benefit. However, the contribution of placebo effect and other forms of study biases in non-randomized studies should not be underestimated. In this context, the true efficacy of VNS as a palliative measure for epilepsy patients remains an open question.

While significant efforts were invested to ensure rigor in the study design of the various RCT reviewed here, challenges intrinsic to the study of epilepsy present caveats in the interpretation of the published results. Seizures occur at random times, and confirmation of ictal events by an unbiased observer for the study period is nearly impossible. Reliance on self-reported seizure diaries is the standard of practice in epilepsy investigations. However, such self-reported events are subject to the influences of detection and performance biases, especially if the patient experiences perceived side-effects related to VNS stimulation. Moreover, 5 of the 7 studies were supported by the VNS manufacturer, Cyberonics, Inc;[25-28,31] And, sponsorship of studies by the manufacturing company has the potential to influence the conclusions of a study.[35] That said, such findings have not been recapitulated for neurosurgical RCTs specifically.[36] Confirmation of the efficacy of VNS in the 2 non-industry sponsored studies provides further reassurance.

In sum, our interpretation of the available literature supports the efficacy of VNS for medically intractable epilepsy as a palliative measure. Since initial FDA approval, VNS technology has evolved dramatically. Newer generation implantable pulse generators now provide the option for cardiac-triggered stimulation, automatic changes in planned changes in stimulation parameters, and the integration of event detection monitoring which aids in therapeutic optimization.[37] In parallel with these advances, latest generation implantable pulse generators are physically smaller than the original device and have significantly longer battery life. Our analysis of the literature raised several key questions that await future investigations, including development of biomarkers for identification of seizure patients who are most likely to benefit from VNS as well as resolving the discrepancy between efficacy of VNS in RCTs when compared

to "real world" experiences. Efficacy of VNS as an adjunct treatment to the latest generation of neuro-modulatory therapeutic platforms, such as deep brain stimulation and responsive neural stimulation, also warrants investigation. Finally, advances in wearable devices, such as smartwatches, have the potential to bypass the need for patient reported seizure diaries in future clinical studies. The development of "closed-loop VNS" systems[38] and transcutaneous VNS as adjunctive treatments for medically intractable epilepsy has the potential to further enhance the efficacy of VNS in select patients.

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