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Vagus nerve stimulation therapy for partial-onset seizures

A randomized active-control trial

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Article abstract—*Objective:* The purpose of this multicenter, add-on, double-blind, randomized, active-control study was to compare the efficacy and safety of presumably therapeutic (high) vagus nerve stimulation with less (low) stimulation. *Background:* Chronic intermittent left vagus nerve stimulation has been shown in animal models and in preliminary clinical trials to suppress the occurrence of seizures. *Methods:* Patients had at least six partial-onset seizures over 30 days involving complex partial or secondarily generalized seizures. Concurrent antiepileptic drugs were unaltered. After a 3-month baseline, patients were surgically implanted with stimulating leads coiled around the left vagus nerve and connected to an infraclavicular subcutaneous programmable pacemaker-like generator. After randomization, device initiation, and a 2-week ramp-up period, patients were assessed for seizure counts and safety over 3 months. The primary efficacy variable was the percentage change in total seizure frequency compared with baseline. *Results:* Patients receiving high stimulation (94 patients, ages 13 to 54 years) had an average 28% reduction in total seizure frequency compared with a 15% reduction in the low stimulation group (102 patients, ages 15 to 60 year; $p = 0.04$). The high-stimulation group also had greater improvements on global evaluation scores, as rated by a blinded interviewer and the patient. High stimulation was associated with more voice alteration and dyspnea. No changes in physiologic indicators of gastric, cardiac, or pulmonary functions occurred. *Conclusions:* Vagus nerve stimulation is an effective and safe adjunctive treatment for patients with refractory partial-onset seizures. It represents the advent of a new, nonpharmacologic treatment for epilepsy.

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Despite advances in medical and surgical therapies, poorly controlled partial-onset seizures remain a major clinical problem, affecting approximately 150,000 to 300,000 people in the United States.[1,2] Patients with refractory epilepsy experience reduced quality of life, increased injuries, and excessive mortality compared with age-matched peers.

One alternative therapy for refractory epilepsy involves electrical stimulation of selective cerebral regions. This approach is supported by observations in

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animal models that electrical stimulation of particular brain areas suppresses seizure occurrence.[3-9] These observations have led to experimental cerebellar and thalamic stimulation for epilepsy.[10-13]

Electrical stimulation of the extracranial vagus nerve in animals has been shown to cause electroencephalographic changes and to induce early-immediate gene expression in brain.[14-17] Vagus nerve stimulation in humans alters blood flow within certain brain areas.[18,19] Notably, vagus nerve stimulation suppresses experimental seizures in several species.[20-25] Pentylenetetrazol-induced, maximal electroshock-induced, and penicillin-induced epileptiform activity are suppressed by vagus nerve stimulation.[22,24] Stimulation of the vagus nerve in the first seconds of a pentylenetetrazol seizure aborts the ictal event.[24] These observations indicate that vagus nerve stimulation significantly affects cerebral activity and has potential use for epilepsy. The precise vagal antiepileptic mechanism is unknown but can be reasonably assumed to involve brainstem nuclei. The nucleus of solitary tract, the main terminus for vagal afferents, has direct or indirect projections to locus coeruleus, raphe nuclei, reticular formation, and other brainstem nuclei.[26-29] These nuclei have been shown to influence cerebral seizure susceptibility,[4-8] hence vagal modulation of one or more of these nuclei could plausibly represent the mechanism for seizure suppression.[25]

Prior clinical studies have indicated that vagus nerve stimulation is capable of safely suppressing seizures in humans.[30-37] We report efficacy and safety of vagus nerve stimulation in a large U.S. multicenter, double-blind, active-control, add-on trial for refractory partial-onset seizures. We hypothesized that patients receiving high vagus nerve stimulation would show a greater seizure reduction than patients receiving low vagus nerve stimulation. This study represents the largest prospective controlled trial of a device for the treatment of epilepsy ever conducted.

Methods. *Protocol.* We studied 254 patients with medically refractory partial-onset seizures. Patients were eligible if they had at least six partial-onset seizures involving alteration of consciousness (complex partial or secondarily generalized convulsions) over 30 days, with no more than 21 days between seizures. Patients could also have other seizure types. Patients were required to submit accurate seizure counts, with or without the assistance of a caregiver, be age 12 to 65 years, use acceptable contraception if female and fertile, and take one to three marketed antiepileptic drugs on a stable regimen for at least 1 month or five half-lives plus 2 weeks (whichever was longer) before study entry.

Patients were excluded for deteriorating neurologic or medical conditions, pregnancy, cardiac or pulmonary disease, active peptic ulcer, history of nonepileptic seizures, more than one episode of status epilepticus in the previous 12 months, prior cervical vagotomy, inability to give proper consent, prior vagus nerve stimulation, prior brain stimulation, resective epilepsy surgery, or inability to perform pulmonary function tests or comply with clinic visits. The protocol was approved by the Institutional Review Board at each institution, and informed consent obtained from all patients or their caregivers.

The study was divided into *baseline* and *treatment* phases. During the 12- to 16-week *baseline*, patients were evaluated at four clinic visits. Patients kept daily seizure records and reported adverse symptoms and medications. Complex partial, secondarily generalized, and simple partial seizures with motor manifestations were recorded and counted but simple partial seizures that lacked an observable motor component were not. Primarily generalized seizures were also recorded. Antiepileptic drugs were not changed, except as necessary to maintain appropriate concentrations or in response to apparent drug toxicity.

After visit 4, patients meeting protocol eligibility requirements underwent implantation of the vagus nerve stimulation device (NeuroCybernetic Prosthesis, Cyberonics, Inc., Webster, TX). During the procedure, coiled stimulation leads were placed around the left vagus nerve and connected subcutaneously to a generator placed below the clavicle.[38] Intraoperatively, the system leads and generator functions were verified, and the output programmed to zero current. Lead location was verified after surgery with a radiograph. Once implanted, the system could be interrogated and programmed during clinic visits by an external programming wand connected to a computer and held over the device.

The *treatment* phase began when stimulation was initiated 2 weeks after implantation, on visit 5. Patients were randomly assigned to high or low stimulation. The high-stimulation group received stimulation thought from previous studies to be most effective, with on/off cycles of 30 seconds every 5 minutes, each "on" period consisting of 500-μs duration pulses at 30-Hz frequency. On initiation, the current was increased over 24 hours by a designated unblinded programmer at each site, from zero to a level perceived by the patient, yet tolerated. At a subsequent visit 2 weeks later (visit 6) and at three more visits over 12 to 16 weeks (visits 7 to 9), the current could be increased as tolerated but could not exceed 3.5 mA. High-stimulation group patients could also manually activate the device using a handheld magnet to produce a 30-second stimulation "on" period in an attempt to abort a seizure.

The low-stimulation group received stimulation believed to be less effective and thus represented an active-control group. Because patients perceive vagal stimulation, the study design incorporated an active-control group rather than a placebo group. It was not assumed that low stimulation was ineffective; the hypothesis was that the high-stimulation group would have more seizure reduction than the low-stimulation group.

Low-stimulation patients received stimulation on/off cycles of 30 seconds every 3 hours, with each "on" cycle consisting of 130-μs duration pulses at 1-Hz frequency. On initiation of stimulation at visit 5, the current was increased to the point of patient perception; on subsequent visits, the device was interrogated, as with high-stimulation patients, but the current was not increased. Although the patient could attempt to abort seizures with the magnet, the device was programmed so that the magnet did not activate the device.

At each visit during the treatment period, patients sub-

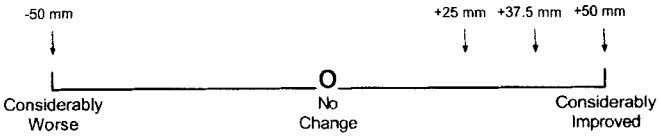

Figure 1. General evaluation well-being scale. The blinded interviewer, patient, or companion placed an "X" on the scale at each visit after visit 1, rating the current well-being compared with that of visit 1. Arrows *denote measures on the scale; these annotations were not part of the study scale. The +25 mm and +37.5 mm points are indicated; an "X" at or to the right of these points indicates the perception of a substantial improvement.*

mitted seizure counts and information on adverse events. At the end of the treatment phase, all patients were eligible to enter an open-treatment extension protocol.

On each visit after visit 1, the blinded interviewer, patient, and patient's companion compared the quality of life relative to visit 1, marking a visual analog scale with an "X." The ends of the scale represented considerably worse (at minus 50 mm) or considerably improved (plus 50 mm), whereas the midpoint of the scale (0 mm) represented no change (figure 1). At the end of baseline and treatment, quality-of-life and cognitive tests were administered; these are the subject of a separate report.

Safety evaluations included adverse symptoms, vital signs and weight, general physical and neurologic examination, plasma antiepileptic drug concentrations, serum hematology and chemistry, and urinalysis. Potential autonomic effects of vagal stimulation were assessed by fasting serum gastrin, Holter monitoring, and pulmonary function tests.

Treatment could be stopped at the patient's request or if in the judgment of the treating physician the continued presence of the device or of stimulation posed a potential risk.

Statistical analysis. The primary outcome variable was the percentage change in total seizure frequency during the treatment period relative to the baseline period (visits 1 to 4). The primary analysis was a between-groups comparison (high-stimulation versus low-stimulation) of the primary outcome variable. Treatment-phase efficacy analysis was performed on seizures occurring in the 3 months after the 2-week ramp-up period between visits 6 and 9; patients not receiving any stimulation during this period were not included in the efficacy analysis. If a subject withdrew during treatment, only the efficacy data during stimulation were used, provided that the patient met eligibility requirements up to withdrawal. A sample of 100 patients in each treatment group was prospectively planned to detect a difference in mean primary outcomes of 15%, with 0.80 power and alpha set at 0.05.

Secondary efficacy measures included between-group comparisons of seizures involving alteration of awareness, within-group changes in seizure frequency during treatment relative to baseline, and numbers of patients responding with 50% or 75% seizure-frequency reductions.

Global evaluation scores of patient well-being, as rated by the blinded interviewer, patient, and companion, were analyzed with both between-groups and within-group comparisons.

All implanted patients were included in the statistical analyses of adverse events. Serum gastrin, Holter monitor-obtained cardiac data, pulmonary function values, serum antiepileptic drug levels, vital signs, and body weights were analyzed for changes from baseline by both between-groups and within-group comparisons.

The Aligned Ranks nonparametric test, a modified Mantel-Haenszel test that adjusts for multiple centers,[39] was chosen prospectively in consultation with the Federal Drug Administration as the primary statistical analysis for the primary efficacy endpoint. Analysis of variance and Student's *t*-test were chosen prospectively to supplement the primary analysis; in addition, the Wilcoxon signed-ranks nonparametric test was to be used if the assumption of normality did not hold. For within-group analyses, the paired *t*-test for normal data or the Wilcoxon signed-ranks for non-normal data was used. Chi-square or Fisher's exact tests were applied to compare responder rates, incidence of treatment-emergent adverse events between groups, and proportions with global well-being ratings at +25 and +37.5 mm between groups. McNemar's test for matched pairs with dichotomous outcomes was used to compare in a paired fashion within a treatment group the incidence of adverse events reported in baseline with those reported during stimulation. All tests of statistical significance were two-tailed; alpha was set at 0.05.

Assignment. A randomization schedule was generated by a statistical consultant before study initiation. A consultant organization not connected to the sponsor, to the data analysis consultant organization, or to any study site served as central randomizer, using this randomization schedule. Randomization for each study site was in groups of four patients (two high-stimulation, two low-stimulation). When a study patient attained visit 5, the unblinded programmer at that site telephoned the randomizer to obtain the randomized treatment assignment. The blinded interviewer at each site had no access to the randomizer, nor to the treatment assignment list, which was kept in a locked place by the site programmer.

Blinding. To maintain blinding, at each treatment-phase visit the device was temporarily turned off while the patient was assessed by the blinded interviewer. Patients were not given details about the high- and low-stimulation cycles and were instructed to not inform blinded personnel how often the device came on and to not discuss their experiences with other patients. An independent monitoring corporation monitored the study and ensured adherence to protocol and blinding procedures. The study data were analyzed by a data analysis consultant firm not connected to the sponsor. All patients completed their study participation, and all primary and secondary analysis was completed before breaking of the study code.

Results. *Participant flow.* From January 31, 1995, to August 29, 1996, 254 patients participated in the study at 20 U.S. centers (figure 2). Of these, 55 patients were discontinued from baseline, usually for failing protocol eligibility, and one patient was implanted but not randomized because of device-related infection. Of 198 randomized patients, one patient produced unevaluable seizure calendars during the treatment phase and a second patient withdrew consent during ramp-up before the treatment efficacy period because of adverse symptoms. Data from these two patients were included in safety analyses. Data from the remaining 196 patients were used for intent-to-treat effi-

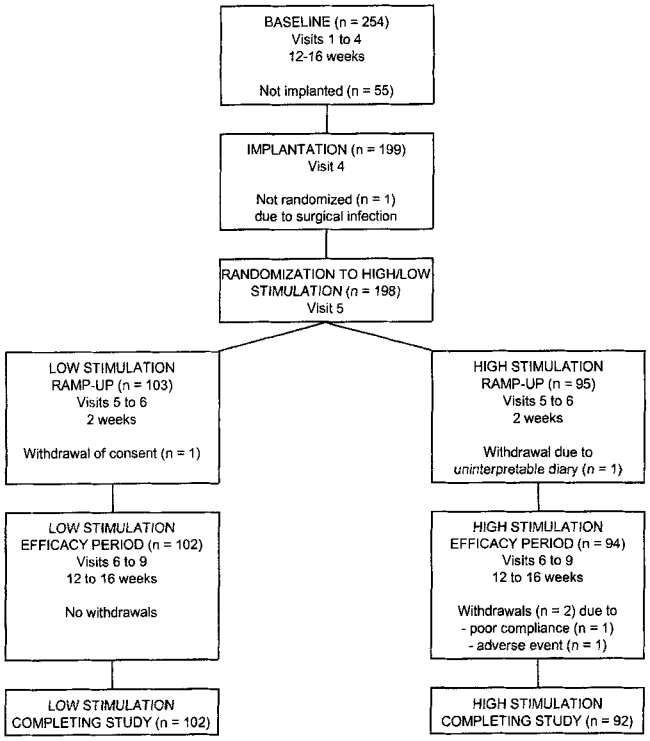

Figure 2. Participant flow.

cacy analyses. Of these, 194 completed the study. Two had stimulation discontinued on visit 7—one because of lack of compliance and the other because of adverse symptoms.

Analysis. The high- and low-stimulation groups were comparable regarding demographic and pretreatment seizure characteristics (table 1). Baseline total seizure frequency and seizure subtype frequencies did not differ significantly between the two groups. The study population had long-duration epilepsy (average, 23 years), with high seizure frequency despite multiple previous medication trials.

Seizure frequency. Patients receiving high stimulation had a mean 27.9% decrease in total seizure frequency relative to baseline (table 2), whereas low-stimulation patients had a mean 15.2% decrease. Between-group analysis indicated significance with the nonparametric Aligned Ranks test ($p = 0.04$) and the t-test ($p = 0.02$). In addition to total seizure frequency, high-stimulation patients had more reduction of partial-onset seizures with alteration of awareness (complex partial seizures plus secondarily generalized convulsions) than did low-stimulation patients ($p = 0.03$, Aligned Ranks; $p = 0.02$, t-test). High-stimulation patients were also more likely to achieve a 75% reduction in seizures ($p = 0.015$, Fisher's exact test). Between-group comparison for 50% responders was not statistically significant ($p = 0.172$, chi-square). One high-stimulation patient was seizure-free during the 3-month treatment efficacy period.

Within-group tests revealed that high-stimulation patients had a significant reduction in frequency of total seizures ($p < 0.0001$; Wilcoxon, t-test) and of partial-onset seizures involving alteration of awareness ($p < 0.0001$; Wilcoxon, t-test), compared with baseline (see table 2). The low-stimulation group also experienced a reduction of total seizures ($p < 0.0001$, Wilcoxon; $p < 0.0002$, t-test) and of partial-onset seizures with alteration of awareness ($p = 0.0001$, Wilcoxon; $p = 0.001$, t-test).

Table 1 *Characteristics of the patients with medically refractory partial-onset seizures, according to treatment group*

Characteristic	Low, n = 103	High, n = 95
Age (y)		
Mean ± SD	34.2 ± 10.1	32.1 ± 10.8
Range	15–60	13–54
Gender, n (%)		
Male	44 (42.7)	49 (51.6)
Female	59 (57.3)	46 (48.4)
Race, n (%)		
White	86 (83.5)	85 (89.5)
Hispanic	10 (9.7)	7 (7.4)
Other	7 (6.8)	3 (3.1)
Total seizure frequency per day during baseline		
Median	0.51	0.58
Mean ± SD	0.97 ± 1.13	1.59 ± 3.26
Partial-onset seizures with alteration of awareness		
Per day during baseline		
Median	0.49	0.51
Mean ± SD	0.83 ± 0.94	1.21 ± 1.96
Number of antiepileptic drugs, mean ± SD		
Taken at time of enrollment	2.1 ± 0.7	2.2 ± 0.7
Previously tried and discontinued	5.7 ± 2.5	5.0 ± 2.3
Years of seizure disorder, mean ± SD	23.7 ± 10.8	22.1 ± 11.5
Range	2–52	2–48

Retrospective analysis indicated that high-stimulation patients without auras had as much seizure frequency reduction (average, 27.4%) as high-stimulation patients with auras (average, 28.6%), indicating that the presence or lack of reported aura is not a predictor of vagus nerve stimulation efficacy.

Global evaluations. Global evaluations of patient well-being were stable during baseline and after implantation, then improved with vagus nerve stimulation (figure 3). Within-group comparisons of the scores at each of visits 7 to 9 of the treatment period with visit 1 of the baseline were significant for evaluations performed by the blinded interviewer, patient, and companion in both groups, indicating perceived improvement of patient well-being ($p < 0.001$, within-group t-test).

The mean score at treatment visits 7 to 9 was rated by the blinded interviewer as higher for high-stimulation patients than for low-stimulation patients ($p = 0.02$, t-test). The mean difference between high-stimulation and low-stimulation ratings by the interviewer was 4.0 mm, with 95% CI 0.6 to 7.4 mm. The ratings by the blinded patients were higher for the high-stimulation group than for the low-stimulation group, with a mean difference of 6.6 mm

Table 2 *Seizure frequency in patients with partial-onset seizures during* low *or* high *vagus nerve stimulation*

Variable	Low	High
Patients (n)	102	94
Change in total seizure frequency from baseline (%)		
Mean ± SD	−15.2 ± 39.2	−27.9 ± 34.3
Mean difference and 95% CI	—	−12.7 (−2.3, −23.1)
Between-groups p value (aligned ranks)	—	0.04
Within-group p value (Wilcoxon)	<0.0001	<0.0001
Change in partial-onset seizures (%)		
With alteration of consciousness		
Mean ± SD	−13.4 ± 40.1	−26.6 ± 36.8
Mean difference and 95% CI	—	−13.2 (−2.3, −24.1)
Between-groups p value (aligned ranks)	—	0.03
Within-group p value (Wilcoxon)	<0.0001	0.0001
Patients with reduction in seizure frequency, n, %		
50% or more	16 (15.7)	22 (23.4)
75% or more	2 (2.0)	10 (10.6)*

* $p = 0.015$, Fisher's exact test.

with 95% CI 2.2 to 11.0 mm ($p = 0.004$, t-test). Companions rated both high-stimulation and low-stimulation patients as improved; the between-group comparison was not statistically significant.

During treatment, interviewers rated more high-stimulation patients than low-stimulation patients at +25 mm or more ($p = 0.01$, Fisher's exact test) and at +37.5 mm or more ($p = 0.02$). More high-stimulation patients than low-stimulation patients rated themselves at +37.5 mm or more ($p < 0.05$) but for +25 mm or more, the difference was borderline significant ($p = 0.08$).

Safety. Surgery-related complications included left vocal cord paralysis in two patients, lower facial muscle paresis in two patients, and fluid accumulation over the generator requiring aspiration in one patient. All these complications resolved. Infection around the device occurred in three patients, leading to device removal before randomization, at visit 7, or after study completion. The patient whose device was removed at visit 7 was reimplanted and finished the study.

The average final current setting was 1.3 mA for high-stimulation patients and 1.2 mA for low-stimulation patients. Although these current settings are comparable, low-stimulation patients received less stimulation because pulse frequency and duration were less.

Adverse symptoms reported by patients during stimulation are shown in table 3. High-stimulation patients were more likely to report voice alteration and dyspnea. The blinded interviewer was more likely to judge a reported symptom as related to stimulation in high-stimulation patients than in low-stimulation patients in the case of voice alteration (47.4% versus 9.7%), dyspnea (11.6% versus 1.0%), or pharyngitis (15.8% versus 3.9%). Although the incidence of paresthesia and cough did not differ between groups, within-group analyses indicated that these symptoms were more common during treatment than in baseline in both groups (see table 3). With the exception of one low-stimulation patient, these symptoms were rated as mild or moderate, were well-tolerated, and did not require a reduction in stimulation. Statistical analyses did not reveal the emergence of central nervous system adverse events in either group.

Of 198 patients implanted with the device and randomized, two were discontinued from the study because of adverse events. One high-stimulation patient had postictal Cheyne-Stokes respiration; this symptom recurred after device deactivation. This patient's device was subsequently restarted during the extension study without sequelae. One low-stimulation patient reported a variety of symptoms during ramp-up and was discontinued from the study; as similar symptoms occurred before and after study participation, they were judged by the investigator as unrelated to vagus nerve stimulation treatment.

Between-group and within-group analyses did not show changes with treatment in serum chemistry or hematology, urinalysis, weight, or vital signs (blood pressure, respiratory rate, heart rate, temperature). Autonomic function assessments revealed no significant changes in serum gastrin, Holter function measures (mean heart rate, mean lowest or highest heart rate, heart rate variability, occurrences of bradycardia), or pulmonary function measures. There were no abnormalities suggestive of an idiosyncratic allergic reaction to the device and no device malfunctions.

Concurrent antiepileptic drug treatment. The pattern of antiepileptic drug use did not differ significantly between the two groups for any drug, nor the proportion with a medication change 1 month before study entry. No significant within-group or between-group changes in serum concentration occurred for any antiepileptic drug during the study.

Discussion. The results of this trial demonstrate that left vagus nerve stimulation is an effective and safe adjunctive treatment for refractory partial-onset

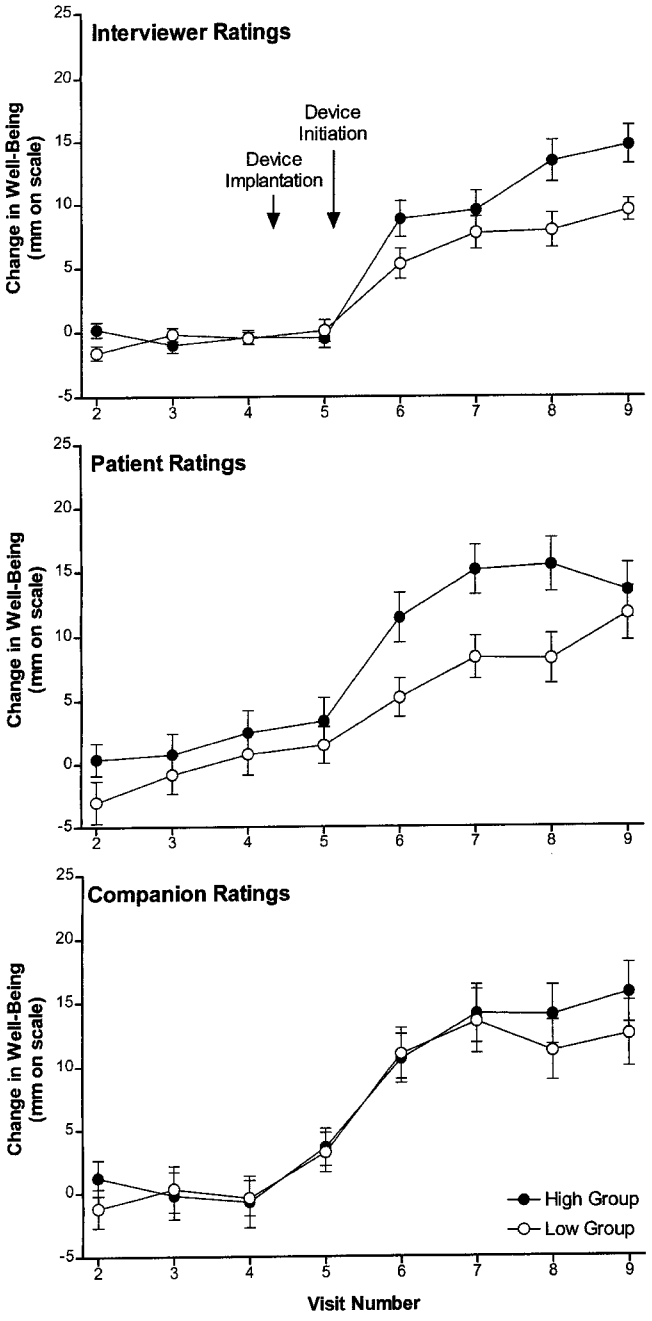

Figure 3. Change in general evaluation of overall well-being at each visit compared with the first visit of baseline. Means and standard errors of the mean are shown. Patients receiving high stimulation were rated as having more improved well-being during stimulation than were patients receiving low stimulation by the interviewer (p = 0.02, t-test) or by themselves (p = 0.004, t-test). Companions did not rate high-stimulation patients as more improved than low-stimulation patients.

seizures. Compared with low stimulation, high stimulation significantly reduced overall seizure frequency. Also observed was a reduction in partial-onset seizures involving alteration of awareness (complex partial plus secondarily generalized convulsions), an important observation because these seizures have a greater impact on patient safety, ability, and quality of life than simple partial seizures. High stimulation also improved global assessments of well-being more than low stimulation, as judged by the blinded interviewer and patient. This efficacy was demonstrated in a group of epileptic patients with long-standing, highly refractory seizures despite many trials of medications.

***Table 3** Treatment phase adverse events among patients treated with* low *or* high *vagus nerve stimulation**

Adverse event	Low, n = 103	High, n = 95
Voice alteration	31 (30.1)	63 (66.3)‡
Cough	44 (42.7)§	43 (45.3)§
Pharyngitis	26 (25.2)	33 (34.7)
Pain	31 (30.1)	27 (28.4)
Dyspnea	11 (10.7)	24 (25.3)†
Headache	24 (23.3)	23 (24.2)
Dyspepsia	13 (12.6)	17 (17.9)
Vomiting	14 (13.6)	17 (17.9)
Paresthesia	26 (25.2)§	17 (17.9)§
Nausea	21 (20.4)	14 (14.7)
Accidental injury	13 (12.6)	12 (12.6)
Fever	19 (18.4)	11 (11.6)
Infection	12 (11.7)	11 (11.6)

Values are numbers with percentages in parentheses.

* Only adverse events that occurred in more than 10% of high-stimulation patients are listed.
† $p = 0.007$, between-groups comparison, chi-square test.
‡ $p = 0.001$, between-groups comparison, chi-square test.
§ $p < 0.0001$, within-group, McNemar's test for matched pairs with dichotomous outcomes.

Side effects of vagus nerve stimulation were mostly attributable to vagal innervation of the larynx. Voice change, throat paresthesia, dyspnea, cough, and throat discomfort occurred only during "on" current periods. Symptoms could readily be reduced to tolerable levels by adjusting the generator settings before the patient left the clinic; it was rarely necessary to lower the current intensity subsequent to any clinic adjustment. Cough and throat discomfort, if present on leaving the clinic, usually resolved spontaneously within days after the clinic visit. Dyspnea, if present, was generally noticed only during physical exertion. Voice change and throat paresthesia were well tolerated. Vagus nerve stimulation did not cause cognitive, sedative, visual, affective, or coordination side effects. Thus, vagus nerve stimulation differs from currently available antiepileptic drugs by possessing a unique and favorable side-effect profile that avoids cerebral toxicity.

Not surprisingly, vagus nerve stimulation had no effect on concurrent antiepileptic drug serum levels or on body chemistry. Conversely, vagal efferent innervation of the heart, lungs, and stomach posed an important safety issue. Rigorous blinded collection of autonomic measures revealed no effect of vagal stimulation on weight, serum gastrin, Holter monitor indicators of cardiac function, or pulmonary function

tests. These results indicate that electrical stimulation of the left vagus nerve, administered at levels that do not exceed comfort, has no demonstrable adverse effect on vagus-mediated visceral functions. This conclusion cannot be extrapolated to the right vagus nerve; only left-sided stimulation was assessed.

Our results validate indications from previous investigations that vagus nerve stimulation for epilepsy is effective and safe.[30-37] The results may be compared with those of an international study[36] that included all simple partial seizures in seizure counts, whereas this study excluded nonmotor simple partial seizures. This study also differed in excluding patients with prior cerebral surgery for epilepsy, using an adverse event checklist at each visit, rigorous physiologic testing, and an independent monitoring organization. In the previous study, the mean total seizure reduction was also significantly reduced in the high-stimulation group (24.5%), compared with a low-stimulation group (6.1%; $p = 0.01$). The high-stimulation group in the international study had a higher number of 50% responders than did low-stimulation patients (31% versus 13%, $p = 0.02$), whereas in this study, a between-group difference was found for 75% responders but not for 50% responders.

This trial represents an application of a rigorous drug-study type of design to the assessment of safety and efficacy of a device for epilepsy. Several aspects of the study were designed to optimize seizure counts as a reliable and valid measure of seizure control. To qualify, patients had to have a high frequency of partial-onset seizures involving loss of awareness, yet have no more than one episode of status epilepticus in the past year. Nonmotor auras were omitted from seizure counts to avoid excessive variability. To preserve blinding of the patient and of assessing medical personnel, an active-treatment control group was used, in which control patients were treated in identical fashion but received less frequent stimulation than a high-stimulation treatment group.

A striking result of this study was a high completion rate; of 196 patients who were implanted and randomized, 194 (99%) completed the study. This high completion rate reflects tolerability of vagus nerve stimulation by patients. Another indication of acceptance was a notable increase in perceived well-being (see figure 3).

This study was designed to assess whether vagus nerve stimulation exerts efficacy in suppressing seizures and therefore entailed the incorporation of an active-control group. The results shown in table 2 cannot be used to quantitate the efficacy of vagus nerve stimulation because it cannot be assumed that the low-stimulation group is a placebo group. In addition, results of open-extension studies suggest that efficacy improves during the first 12 to 18 months of vagus nerve stimulation therapy,[32,40] hence the first 3 months of therapy may not be representative of achievable control.

Vagus nerve stimulation represents the advent of electrophysiologic stimulation as a new treatment option in the management of refractory partial-onset seizures. Efficacy in the treatment of primarily generalized epilepsy and Lennox-Gastaut syndrome has been reported in open studies.[34,35,41,42] It remains to be fully assessed whether vagus nerve stimulation is effective for severe childhood epilepsy or for genetic epilepsies. These questions, as well as the elucidation of the precise mechanism of action and modifications to improve efficacy, as well as require further investigation.

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