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Automatic Vagus Nerve Stimulation Triggered by Ictal Tachycardia: Clinical Outcomes and Device Performance—The U.S. E-37 Trial

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Objectives: The Automatic Stimulation Mode (AutoStim) feature of the Model 106 Vagus Nerve Stimulation (VNS) Therapy System stimulates the left vagus nerve on detecting tachycardia. This study evaluates performance, safety of the AutoStim feature during a 3-5-day Epilepsy Monitoring Unit (EMU) stay and long- term clinical outcomes of the device stimulating in all modes.

Materials and Methods: The E-37 protocol (NCT01846741) was a prospective, unblinded, U.S. multisite study of the AspireSR® in subjects with drug-resistant partial onset seizures and history of ictal tachycardia. VNS Normal and Magnet Modes stimulation were present at all times except during the EMU stay. Outpatient visits at 3, 6, and 12 months tracked seizure frequency, severity, quality of life, and adverse events.

Results: Twenty implanted subjects (ages 21–69) experienced 89 seizures in the EMU. 28/38 (73.7%) of complex partial and secondarily generalized seizures exhibited $\geq$20% increase in heart rate change. 31/89 (34.8%) of seizures were treated by Automatic Stimulation on detection; 19/31 (61.3%) seizures ended during the stimulation with a median time from stimulation onset to seizure end of 35 sec. Mean duty cycle at six-months increased from 11% to 16%. At 12 months, quality of life and seizure severity scores improved, and responder rate was 50%. Common adverse events were dysphonia ($n = 7$), convulsion ($n = 6$), and oropharyngeal pain ($n = 3$).

Conclusions: The Model 106 performed as intended in the study population, was well tolerated and associated with clinical improvement from baseline. The study design did not allow determination of which factors were responsible for improvements.

Keywords: AspireSR, ictal tachycardia, vagus nerve stimulation, VNS therapy system

Conflict of Interest: Robert S. Fisher, MD, PhD, was a paid consultant and speaker for Cyberonics prior to April 2014. Pegah Afra, MD has received support from Cyberonics for conducting the E-37 Clinical study. Michael P. Macken, MD, has served as a paid consultant and speaker for Cyberonics and received support from Cyberonics for conducting the E-37 Clinical study. Daniela N. Minecan, MD, has received support from Cyberonics for conducting the E-37 Clinical study. Anto Bagic, MD, PhD, has received support from Cyberonics for conducting the E-37 Clinical study. Selim R. Benbadis, MD, has served as a paid consultant and speaker for

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INTRODUCTION

The Vagus Nerve Stimulation (VNS) Therapy System has been shown to be effective for reducing the number of seizures in people with partial and secondarily generalized seizures (1–4). In initial clinical trials, the left vagus nerve was stimulated in ongoing cycles of 30 sec, followed by a periods of no stimulation for 5 minutes. A feature was provided to the subjects for user-initiated stimulation where they or their caregiver could pass a magnet across the implanted device in the chest at the time of the perceived seizure onset. Use of the VNS Manual Magnet Mode feature has been reviewed (5–7). A weighted average of studies showed self-reported or caregiver-reported benefit for 45% of the users, with seizure cessation in 28% (range 15–67%). Patients also reported decreased intensity or duration of seizures or lessening of the post-ictal period when using the Manual Magnet Mode (6,8–10).

Manual application of the magnet at the time of the perceived seizure onset may not be feasible for a variety of reasons. The magnet might not be readily available, the patient may be immobilized by the seizure (11) or cognitively impaired, the seizure could occur during sleep, or the patient might not be aware of the seizure occurrence (12). Therefore, an automated method to initiate stimulation at the start of a seizure could be beneficial. Research supports the occurrence of the phenomenon of ictal heart rate increases based on studies using concurrent electroencephalography (EEG) and electrocardiogram (ECG). Therefore, one strategy to deliver stimulation is to use heart rate changes as a trigger. Approximately two-thirds of focal onset seizures are associated with tachycardia (13). The recently FDA-approved VNS Model 106 implantable pulse generator can deliver stimulation in response to a selectable increase in heart rate (called Automatic Stimulation Mode or AutoStim), as well as providing traditional VNS system stimulation modes (Normal and Magnet Modes).

The E-37 study evaluates the device performance in a controlled setting of a 3–5 day inpatient video-EEG EMU stay and clinical outcome data associated with all available modes of therapy of the Model 106 generator in a U.S. study with 12 months of observation. The study also assessed all treatment-emergent adverse events, usability of the system, and long-term changes over 12 months from baseline in quality-of-life, anti-seizure drug load, seizure frequency, and seizure severity. A parallel study, denoted E-36 (NCT01325623), was conducted by a separate group of European investigators.

MATERIALS AND METHODS

Protocol E-37 (NCT01846741) is a prospective, unblinded, U.S. multisite study designed to collect data on up to 20 subjects 12 years of age or older treated with the VNS Model 106 (AspireSR® VNS Therapy® System, manufactured by Cyberonics, Inc., Houston, TX, USA). The study was performed in patients who were initiating VNS for standard clinical care. None had been treated with prior VNS therapy. Following implant and recovery, subjects participated in a 3–5 day EMU stay where the AutoStim feature was activated. Automatic stimulations occurring within a 4-min window around the seizure onset were considered "True Positives" for performance purposes. During long-term follow-up, all modes of the VNS Therapy System (Normal, Magnet, and AutoStim) were active.

Entry Criteria

Eligible subjects were those at least 12-year old, in good general health suitable for VNS implantation with a clinical diagnosis of drug-resistant epilepsy with partial onset seizures. Historical EEG and ECG tracings of seizures obtained during video-EEG monitoring or ambulatory EEG recordings of eligible subjects were reviewed for presence of ictal tachycardia in at least one seizure, defined as a heart rate above 100 beats per minute (bpm) during a seizure and at least a 55% increase or 35 bpm increase from baseline. Entry required an average of at least three seizures per month for the three months prior to the screening visit and no seizure-free interval greater than 30 days during those three months. A peak-to-peak *R*-wave amplitude greater than or equal to 0.4 mV had to be recordable from the proposed electrode location in the neck to the proposed generator location in the chest via surface ECG electrodes, with the patient in seven different standing, sitting, and reclining body positions (Supporting Information Fig. S1).

Subjects and caregivers had to be willing and able to complete informed consents and or assents with minimal assistance. Subjects were excluded if they had a prior bilateral or left cervical vagotomy, plans for diathermy, need for a full body MRI during the study, prior implantation of a VNS Therapy System, current treatment by an active implantable medical device, IQ known or estimated to be <70, history of depression requiring hospitalization or suicidality, history of status epilepticus within one year of study enrollment, requirement for cardiac or autonomic disorder medications that would affect heart rate response, a clinically meaningful cardiovascular arrhythmia existing prior to the study or determined by a 24-hour Holter recording obtained during the baseline period, dependence on alcohol or narcotic drugs within the past two-year based on history, any history of psychogenic non-epileptic seizures, pregnant, women of childbearing age unwilling to take a pregnancy test and unwilling to use an approved method of contraception during the study, or enrolled in another investigational study at time of entry.

Baseline Evaluation

The protocol and study materials were approved by Institutional Review Boards prior to enrollment. Potential subjects were screened in a clinic visit and arrangements made to obtain and review prior recorded seizures to verify the presence of ictal tachycardia in at least one seizure. Those enrolled completed baseline evaluation

questionnaires, including the Quality of Life in Epilepsy-Patient-Weighted; QOLIE-31-P for subjects 18 years and older (14), Seizure Severity Questionnaire (SSQ) (15), and the National Hospital Seizure Severity Scale, NHS3 (administered by a physician) (16). Subjects were trained to record seizures by means of a provided seizure diary. Information was collected on medical, anti-seizure drugs, seizure history, seizure type, and frequency. Anti-seizure drug doses and levels were left to the discretion of the investigators throughout the study. Ability to detect an R-wave on the ECG was assayed in seven different physical positions to determine a suitable implant location and guide selection of the heartbeat sensitivity setting of the device. A 24-hour Holter ECG was done to rule out significant arrhythmias.

Device Description

The AspireSR implantable pulse generator is identical in size and shape to the Model 105 AspireHC®. The device under study, however, has onboard heartbeat sensing technology that allows for the detection and monitoring of changes in heart rate. The detection algorithm establishes a baseline (background) heart rate over a period of approximately 5 min as well as a near-term (foreground) heart rate for comparison. Detection occurs when the foreground heart rate exceeds the background heart rate by the threshold programmed by the clinician.

Implantation

The implanted AspireSR VNS Therapy System included an investigational Model 106 implantable pulse generator and a commercial lead, either Model 303 or 304, attached to the left vagus nerve. The AutoStim feature of this device utilizes an algorithm to identify rapid increases in heart rate that may be associated with seizure onset ictal heart rate increase. The handheld programmer obtained a readout of the device-detected heart rate in the operating room and sensitivity was adjusted until it was verified to be within ± 5 b.p.m. or 10% of the ECG monitor in the operating room. Approximately two weeks after surgery, the traditional VNS Normal and manual Magnet Modes were turned on. The initial Normal Mode settings were 0.25 mA (0.50 mA, if tolerated), pulse width 250 μsec (500 μsec, if tolerated), signal frequency 20 Hz, on time 30 sec, off time 5 min, and black-out time 30 sec. Magnet Mode settings were 0.25 mA (0.5 mA, if tolerated), pulse width 250 μsec, on time 60 sec. The output current for AutoStim mode remained at 0 mA. If 0.5 mA stimulation was not tolerated at the two-week visit after surgery, then the amplitude was gradually titrated up to 0.5 mA at an additional visit prior to the start of the EMU admission. Low output currents were chosen for the brief period of time between turning the device on and the beginning of the EMU procedures to limit the therapy delivered to the patient, thereby increasing the chances to record seizures during the EMU stay.

Epilepsy Monitoring Unit Admission

Subjects were admitted to the EMU two–four weeks after device implantation. Decisions regarding medication management (continuation, reduction, or temporary discontinuation) were left to each investigator, depending on the clinical needs for the admission. On admission to the EMU, the VNS Normal Mode was programmed to deliver stimuli at 0.75–1.5 mA, as tolerated, pulse width 250–500 μsec, signal frequency 20 Hz, on time 30 sec, off time 5 min, and Magnet Mode and AutoStim output current to 0 mA for a one-hour time period. After one hour at these settings (used to verify tolerability and correct functioning of the system), AutoStim Mode was programmed on in conjunction with Normal and Magnet modes for two hours. Settings for AutoStim were output current 0.75 mA to 1.5 mA, pulse width 250 μsec to 500 μsec, and on time 60 sec. These settings are consistent with those observed clinically with long-term VNS and described in the application of a computational model of VNS (17). Sensitivity settings of the tachycardia detection algorithm range from 20% to 70% (threshold for AutoStim), with 70% being the least sensitive and 20% being the most sensitive with high nonseizure-related detections (false positives). The threshold for the AutoStim feature was programmed for each subject, based on the historical ictal elevation in heart rate for that subject, requiring the corresponding heart rate elevation above that of a moving baseline window as follows: threshold for AutoStim setting 1, $\geq$70%; 2, $\geq$60%; 3, $\geq$50%; 4, $\geq$40%; 5, $\geq$30%, 6, $\geq$20%. After two hours of recording with all traditional and AutoStim modes on, to evaluate technical compatibility of all modes, Normal and Manual Magnet Modes were turned off and only the AutoStim feature remained on until time of discharge. No unexpected interactions among the different device modes were encountered.

Each day in the EMU, subjects exercised for up to 3 min by stepping up and down at a submaximal effort level on a step stool. Device memory and time stamp logs were downloaded. At time of discharge, all traditional VNS modes and AutoStim were activated. The investigators could select any clinically desired output current provided that the manual magnet mode current did not exceed the AutoStim current; this prevented the magnet mode from superseding an ongoing AutoStim burst and allowed for the effect and performance of AutoStim to be observed.

True positive automatic stimulations were defined as those within a time window 2 min before or after onset of the seizure. AutoStims that occurred outside this 4-min window were considered nonseizure-related detections. Seizures were categorized by percent heart rate change as follows: after seizure onset was determined, the baseline heart rate was averaged over a 30-sec period of time starting 40 sec before the seizure onset. Ictal heart rate was assessed by identifying the maximum heart rate over the course of 30 sec immediately following seizure onset. From this, the percent change was calculated.

Long-Term Follow-Up

Follow-up clinic visits took place three months after discharge and then every six months after implantation. Information was collected at each visit on quality of life, seizure severity, seizure frequency, adverse events, adverse device effects and medication changes, and the device memory was downloaded to log detections.

Statistical Methods

Data from all investigational sites were pooled for analysis. Statistical significance testing and confidence intervals were performed using a 5% two-tailed significance level. For continuous data, analysis of variance with the *F*-test or *t*-test was used for hypothesis testing. When the numbers were small and normality assumptions were violated, a nonparametric signed-rank test was used. For categorical data, the chi-square test was used for testing the difference in proportions. Fisher's exact test was applied in situations where the chi square test was inappropriate because the sample size was less than 5. All statistical analyses were performed using SAS version 9.3.

RESULTS

Twenty-two (22) subjects were screened, of whom twenty (20) subjects (ages 21–69) were implanted with the Model 106 generator.

Table 1. Demographics, Epilepsy, and Seizure History at Baseline (Safety Population; $N = 20$).

Variable	Total, $n = 20$, n (%)
Gender	
Female	12 (60%)
Male	8 (40%)
Race	
White	15 (75%)
Black	2 (10%)
Hispanic of Latino	3 (15%)
Age (years)	
Mean ± SD	35.6 ± 14.1
Median	31
Range	21–69
Age group	
18–29 years	9 (45%)
30–39 years	5 (25%)
40–49 years	2 (10%)
50–59 years	2 (10%)
60 years or older	2 (10%)
Cognitive status	
Normal	14 (70%)
Minimal Impairment	6 (30%)
Time from diagnosis to VNS therapy (years)	
Mean ± SD	21.2 ± 15.3
Median	17
Range	1-52
Previous brain or epilepsy surgery	
No	12 (60%)
Yes	8 (40%)
Etiology	
Idiopathic Partial	8 (40.0%)
Symptomatic Partial	10 (50.0%)
Cryptogenic	2 (10.0%)
Family history of seizures	
No	12 (60.0%)
Yes	8 (40.0%)
Seizures with auras in past 2 months	
No	7 (35.0%)
Yes	13 (65.0%)

No subject discontinued from the trial. All 20 implanted subjects completed 12-month follow-up assessments.

Baseline Visit

Table 1 summarizes the demographics, epilepsy and seizure history of implanted subjects at baseline. Of the 20 patients treated in this study, the majority of study patients were females ($n = 12$, 60%), and Caucasian ($n = 15$, 75%). Most subjects were of normal cognitive status ($n = 14$, 70%). Additionally, the majority of patients had symptomatic partial epilepsy ($n = 10$, 50%), followed by idiopathic partial ($n = 8$, 40%), and cryptogenic ($n = 2$, 10%) etiologies. The mean time to VNS Therapy from epilepsy diagnosis was 21.2 years (range 1–52 years) and 40% had a family history of seizures. Clinical details pertaining to the treated patients are provided in Supporting Information Table S1.

At the baseline visit, the number of subjects reporting seizures (by type) were simple partial seizures for 11 (55%), complex partial seizures without secondary generalization for 18 (90%), complex partial seizures with secondarily generalized tonic-clonic seizures for 6 (30%), generalized tonic-clonic seizures for 2 (10%). The cumulative percentage exceeds 100% because some subjects had more than one seizure type.

Device Performance Phase

During the EMU stay (Table 2), a total of 89 seizures were observed, among 16/20 (80%) subjects. Investigators reported 84 seizures and an additional five were identified by three blinded, independent EEG reviewers. For seizures confirmed by majority vote and new seizures identified during independent review, the earliest identified electrographic onset time and the latest electrographic seizure end time were taken as seizure onset and offset times for analysis purposes.

Approximately 43% (38/89) of all seizures, among 10/16 (62.5%) subjects who experienced seizures in the EMU stay, exhibited $\geq$20% increase in heart rate compared to baseline, representing the lower threshold of the AutoStim feature's detection capability. Only 16% (14/89) of these seizures met the stringent definition of ictal tachycardia used to screen historical seizures prior to protocol entry.

No primarily generalized seizures and only one secondarily generalized seizure were recorded during the study. Simple and complex partial seizures were equally represented. Based on individual historical levels of ictal heart rate increase, the tachycardia detection threshold for the AutoStim feature was set to $\geq$70% above baseline in six subjects, $\geq$60% in four, $\geq$50% in seven, $\geq$40% in two, and $\geq$30% in one subject.

The distribution of seizures showing heart rate increases of a specified amount was: $<$ 20% heart rate increase, 51 seizures; 20–29%, seven seizures; 30–39%, eight seizures; 40–49%, three seizures; 50–59%, eight seizures; 60–69%, four seizures; $\geq$70%, eight seizures. Complex partial seizures were more likely to be associated with higher heart rate increases; 27 of 38 (71%) complex partial seizures, vs. 7 of 37 (19%) simple partial seizures had heart rate increases exceeding 20% (Supporting Information Fig. S2).

Figure 1 shows the sensitivity vs. nonseizure-related stimulation rates using data collected during the EMU, modeled using a validated bench-top simulant, as if the tachycardia detection setting had been set to each of the settings. Using a low threshold, for example a $\geq$20% increase in heart rate, delivers stimulation during a high number of seizures, but it also produces a higher rate of nonseizure-related stimulation (defined as the total number of nonseizure-related detections divided by the total evaluable monitoring time).

The solid blue line shows results for all 89 seizures and the dotted red line for the 38 seizures associated with more than a 20%

Table 2. Summary of Seizures Reported by Investigators and Triple Review.

	All seizures reported by investigators	Additional seizures identified by triple review	ITT seizures: all patients and all seizures
All seizure types	84	5	89
Total partial	76	0	76
Simple partial	37 (44.0%)	0	37 (41.6%)
Complex partial	38 (45.2%)	0	38 (42.7%)
Secondarily generalized	1 (1.2%)	0	1 (1.1%)
Subclinical	8 (9.5%)	1 (20%)	9 (10.1%)
Unclassified seizure	0	4 (80%)	4 (4.5%)

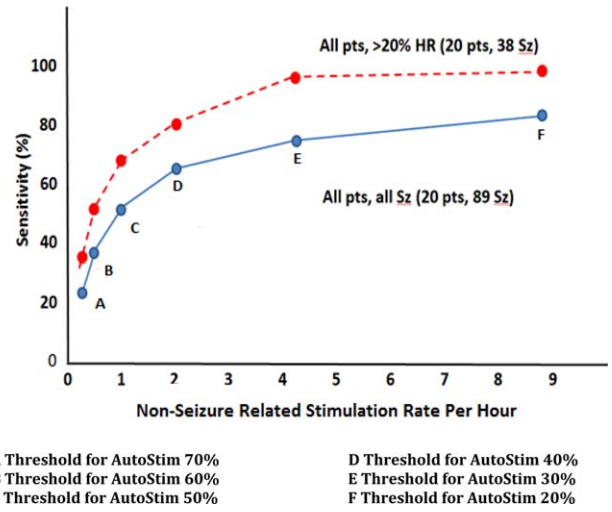

Figure 1. Receiver operating characteristic curves generated from E-37 data postprocessed through a validated bench-top device simulant.

increase in heart rate. Sensitivity (delivery of stimulation during a seizure) only increases slightly by liberalizing the detection criteria to less than a 40% increase over baseline heart rate.

Nonseizure-Related Detection Rate

Nonseizure-detection rate per hour was calculated at the various tachycardia detection settings during EMU, exercise activities (stair stepper), and follow-up visits. Moving from tachycardia detection setting $\geq$40% to $\geq$30% ($n = 1$) raises the nonseizure-related detection rate over sevenfold, but to a number that is still low relative to Normal Mode stimulations that are delivered during a 10% duty cycle (approximately 11 stimulations per hour). Exercise on the stair stepper produced 1.6–6.6 nonseizure-related detections per hour at tachycardia detection settings 30–70% (Supporting Information Table S2).

The addition of the AutoStim feature shows a modest impact on the overall duty cycle when combined with Normal Mode. At three months and six months, with the addition of the AutoStim feature, the duty cycles ranged from 10.6% to 15.9%.

Latency to Detection

Latency was calculated as median, minimum and maximum time between tachycardia detection by the AutoStim feature and seizure onset in relation to the earliest EEG or behavior signs of a seizure. A few of the individual triggered stimulations were before evident seizure onset, but all median latencies ranged from 8 sec to 50 sec after seizure onset. The longest median latency at 50 sec was for the setting that required the highest increase in heart rate (Supporting Information Table S3).

Seizure Cessation

Table 3 shows a summary of seizures treated and terminated during the 60-sec course of AutoStim in the EMU. "Treated" seizures are those seizures that were detected resulting in AutoStim with the Stimulation train overlapping the seizure. "Terminated" seizures are defined as those seizures that ended before AutoStim concluded.

Relationship of Detection Latency to Duration of Seizures

Seizure durations and latencies from stimulation onset to seizure termination were analyzed for all seizures during the EMU stay and for those that did or did not end during AutoStim. Each subject's seizure durations were compared to the durations of his or her historically recorded seizures, for 165 seizures in 19 study subjects. Simple partial seizures that stopped during AutoStim lasted a median of 32 sec, compared to 85 sec (62.4% reduction) for historical comparison simple partial seizures (Table 4). Median seizure duration was similar for complex partial seizures during the trial and for historical recordings (74 sec vs. 80 sec).

Overall, for seizures treated and terminated during AutoStim (19/31; 61.3%; from nine patients), seizures that ended during stimulation, the closer stimulation was to seizure onset, the shorter the seizure duration (Supporting Information Fig. S3). The median time from stimulation onset to seizure end was 35 sec for the terminated seizures.

Long-Term Outcome

Clinical status was assessed at 3, 6, and 12 months, during which the subjects were treated both with the AutoStim feature and traditional VNS therapy. Responders were defined as having at least a 50% reduction in seizures per month compared to baseline. The responder rate was 20% (4/20) at three months, 35% (7/20) at six months and 50% (10/20) at 12 months. Moreover, median percent change from baseline was −19.3% at 3 months, −30.9% at 6 months, and −47.3% at 12 months (Supporting Information Fig. S4).

Figure 2 shows mean seizure severity domain and total scores at 3, 6, and 12 months compared to baseline. Improvements in multiple domains from baseline, including the total score were statistically significant and met the minimum clinical threshold improvement criteria, Minimally Important Change (MIC), for the SSQ scores.

Physician assessments (NHS3) showed a significant reduction in median change from baseline severity for complex partial seizures at 3, 6, and 12 month follow-up visits as (−2.00), (−0.5), and (−1.00). This trend was evident for complex partial seizures with secondary generalization but was not statistically significant, given the small numbers. The median average severity for simple partial seizures did not change over time.

Figure 3 shows the mean QOLIE-31-P scores and domain subscores at 3, 6, and 12 months compared to baseline. All domains with the exception of Energy/Fatigue Final Score were statistically significant and exceeded the MIC criteria for clinical significance at all follow-up visits. The Energy/Fatigue score did however, increase over time and reach statistical significance at the 12-month visit.

To assess a possible contribution of medication changes to improvement in the clinical outcome the Anti-Seizure Drug Load was calculated. The Anti-Seizure Drug load is calculated as the sum of all ratios of the total daily dose of each medication taken on the day of the visit over the defined daily dose of the medication for the main indication according to the WHO database. The median percent increase in drug load was zero (0%) at 3- and 6-month follow-up visits and 3% at the 12-month visit (p = n.s.).

Table 3. Summary of Seizures Treated and Terminated During EMU Stay.

Seizure type	Treated with duration annotated *n/N* (%)
Overall	19/31 (61.3%)
Complex partial seizures	5/12 (41.7%)
Secondarily generalized seizures	0/1 (0.0%)
Simple partial seizures	10/12 (83.3%)
Subclinical seizures	3/4 (75.0%)
Unknown seizures	1/2 (50.0%)

Table 4. Overall Summary of Seizure Duration (Seconds) by Subgroup (ITT Population; Seizures with Annotated Duration).

Seizure type	Statistic	Historical seizures	Terminated seizures during study EMU	Unstimulated seizures* during study EMU
Simple partial seizures	*N*	61	10	2
	Mean (SD)	93.1 (67.0)	38.3 (27.9)	15.5 (16.3)
	Median	85	32	16
	Min, Max	0, 244	7, 75	4, 27
Complex partial seizures	*N*	49	5	15
	Mean (SD)	91.0 (42.2)	81.6 (21.0)	66.9 (43.8)
	Median	80	74	56
	Min, Max	32, 251	62, 115	5, 170
Secondarily generalized seizures	*N*	7	0	0
	Mean (SD)	142.6 (55.3)	—	—
	Median	124	—	—
	Min, Max	103, 263	—	—

*Unstimulated seizures with ≥20% increase in heart rate.

Safety

Use of the Model 106 generator including the AutoStim feature did not produce any unanticipated adverse events. The safety profile observed in the E-37 study was similar to that seen in previous epilepsy studies such as E-05 (18). No new seizure types emerged during the study. The most common adverse events were dysphonia (voice alteration) reported by seven subjects (35%) and convulsion by six subjects (30%), followed by oropharyngeal pain by three subjects (15%). All implantation-related adverse events from the implantation day to 12-month follow-up visit consisted of dysphonia and procedural pain reported by two subjects (10%) each. Stimulation-related adverse events reported from the initial titration visit were dysphonia, reported by six subjects (30%), oropharyngeal pain and dysphagia by two subjects each (10%). Two serious adverse events considered by the investigators to definitely be related to implantation were also reported in different subjects. These consisted of incision wound cellulitis and post-procedural hematomas.

DISCUSSION AND CONCLUSION

The primary findings of the E-37 study were that the device and tachycardia detection algorithm performed as expected and that the device was well-tolerated. The ability to program the Automatic Stimulation mode (AutoStim) to deliver stimulation in response to a ≥20, ≥30, ≥40, ≥50, ≥60, or ≥70% ictal heart rate increase allows individualization of the optimal point on the sensitivity-specificity curve for an individual patient. At least one threshold for AutoStim setting could be chosen to provide >80% sensitivity for detection of all seizures associated with ≥20% ictal heart rate increase. A prior study (19) of cardiac-based VNS therapy in a patient with six seizures recorded with heart-rate-triggered stimulation and six without such stimulation demonstrated a significant reduction of termination time with triggered stimulation. However, our study did not include a control group to allow analysis of effects of AutoStim on seizure duration or characteristics.

To be eligible for the study, participants had to have a previously recorded seizure associated with a heart rate above 100 beats per minute and at least a 55% increase or 35 b.p.m. increase from baseline. Only 14 of the 89 (16%) seizures recorded during monitoring met the strict historically ascertained ictal tachycardia criteria. However, almost half of all seizures (43%; $n = 38$) exhibited ≥20% increase in heart rate compared to baseline, representing the lower threshold of the AutoStims feature's detection capability. This suggests that an AutoStim function would be invoked during a subset of a patient's seizures.

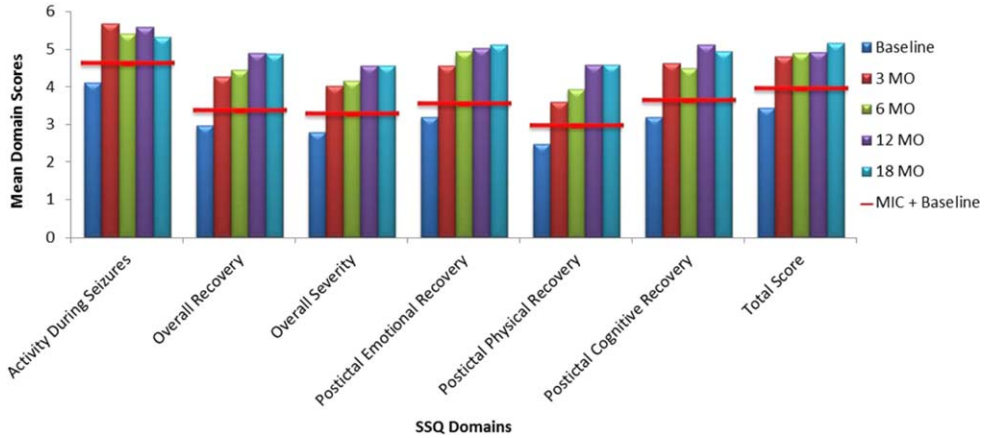

Figure 2. Mean SSQ scores compared to baseline and minimally important change (MIC) criteria by visit (ITT population).

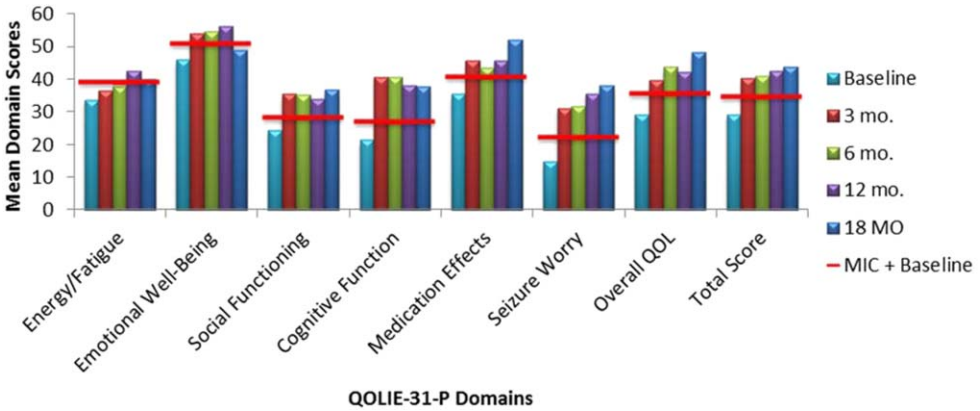

Figure 3. Mean QOLIE-31-P scores compared to baseline and MIC criteria by visit (ITT population).

Ictal heart rate increases associated with seizures may have a different time course from that of heart rate increases associated with nonseizure-related activities (19). Exercise on a step stool produced a modest increase in the nonseizure-related detections. Since the tachycardia detection algorithm utilizes relative increases in heart rate, it is likely that initial rapid rises from a low resting heart rate triggered detection when starting exercise. The number of nonseizure-detection rate decreased during the remaining period of exercise, since an increase in background (average) heart rate decreased the percentage change associated with any transient fluctuations. The extra stimulations did not significantly affect battery life, since measured duty cycles only increased from a baseline of 11% with stimulation to about 16% with Normal Mode, AutoStim, and manual Magnet Mode all on at six months. This is far below the maximal acceptable duty cycle for the VNS therapy system, and below the duty cycle produced by rapid cycling of stimulation (7).

Literature review (13) suggests that about 71% of partial seizures demonstrate ictal increased heart rate, compared to the 43% rate in this study. Simple partial seizures are less likely to show increases in heart rate than are complex partial seizures (20), as confirmed by our observations. The relatively high (42%) prevalence of simple partial seizures in our study might therefore account for the corresponding relatively infrequent occurrence of heart rate increases.

Seizure severity decreased and several indicators of well-being improved over baseline at the 3-, 6-, and 12-month visits. Overall quality-of-life improved more than three times the minimally important clinical criteria. Median percent change from baseline seizure frequency declined over the 3-, 6-, and 12-month visits, consistent with a previous epilepsy study, the PuLsE trial (21). Drug load remained stable throughout the study, as it did in a previous VNS study (21). Hence, observed improvements are not likely due to medication changes.

The small sample size and absence of randomization do not allow conclusions about whether Automatic Stimulation alone, or the combination of Automatic Simulation and Normal Mode VNS therapy, or some other factor was a cause of these beneficial effects. However, the AutoStim feature was well-tolerated and able to function in conjunction with the traditional VNS therapy. The model 106 provides long-term clinical benefits and safety comparable to that of traditional VNS therapy. The performance of the AutoStim mode during the study EMU and the combination use of AutoStim and traditional VNS therapy modes during the long term showed that this feature could be expected to be useful for individuals who exhibit heart rate increases early in at least some of their seizures, who benefit from VNS at the start of a seizure, and who cannot consistently initiate stimulation with a manual magnet.

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Authorship Statements

Robert S. Fisher participated in conception and design of the study, reviewed all of the study data, constructed figures and tables and wrote the first and final drafts of the manuscript. The following authors participated actively in the design of the study in several planning sessions, served as local center principle investigators, reviewed draft manuscripts and contributed changes to the manuscript: Pegah Afra, Micheal Macken, Daniela N. Minecan, Anto Bagić, Selim R. Benbadis, Sandra L. Helmers, Saurabh R. Sinha, Jeremy Slater and David Treiman. Bita Najimipour was the overall study manager for Cyberonics and provided extensive input into study conception, data management and editing the manuscript. Jason Begnaud and Pradheep Raman of Cyberonics supplied data analysis, statistical inferences and editing of portions of the draft manuscript. All authors have read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Listing of Demographic and Epilepsy History per Patient.
Table S2. Nonseizure-related Stimulation Rate Based on Heart Rate Increase Associated with Seizures by Tachycardia Detection Setting: Actual Device Detections During Exercise and Follow-Up Visits (three and six month).
Table S3. Summary of Latency for True Positive Detections by Tachycardia Detection Setting: Actual Device Detections.
Figure S1. Showing the Body with Electrode Placement and 0.4 mV ECG.
Figure S2. Distribution of Simple and Complex Partial Seizures During EMU.
Figure S3. Relationship Between Seizure Detection Latency and Duration, Terminated Seizures from ITT Population.
Figure S4. Median Percent Change from Baseline in Seizure Counts per Month by Visit.

COMMENTS

Control of partial complex seizures with VNS depends, in part, on timely stimulation of the vagus nerve to shorten the seizure interval. Using elevated pulse rates associated with seizure activity to trigger the VNS stimulator is a useful way of improving long-term seizure control. The emergence of Bluetooth wireless technology applied to VNS might be considered in the future for patient comfort and compliance.

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This is a well written paper expanding the field of neuromodulation, with active interface on ictal seizures. This is one of a first generation of devices that will automatically deploy an electroceutical when needed. It is an exciting time in neuromodulation.

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Comments not included in the Early View version of this paper.

