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FULL-LENGTH ORIGINAL RESEARCH

Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy

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Summary

Purpose: We report a multicenter, double-blind, randomized trial of bilateral stimulation of the anterior nuclei of the thalamus for localization-related epilepsy.

Methods: Participants were adults with medically refractory partial seizures, including secondarily generalized seizures. Half received stimulation and half no stimulation during a 3-month blinded phase; then all received unblinded stimulation.

Results: One hundred ten participants were randomized. Baseline monthly median seizure frequency was 19.5. In the last month of the blinded phase the stimulated group had a 29% greater reduction in seizures compared with the control group, as estimated by a generalized estimating equations (GEE) model (p = 0.002). Unadjusted median declines at the end of the blinded phase were 14.5% in the control group and 40.4% in the stimulated group. Complex partial and "most severe" seizures were significantly reduced by stimulation. By 2 years, there was a 56% median percent reduction in seizure frequency; 54% of patients had a seizure reduction of at least 50%, and 14 patients were seizure-free for at least 6 months. Five deaths occurred and none were from implantation or stimulation. No participant had symptomatic hemorrhage or brain infection. Two participants had acute, transient stimulation-associated seizures. Cognition and mood showed no group differences, but participants in the stimulated group were more likely to report depression or memory problems as adverse events.

Discussion: Bilateral stimulation of the anterior nuclei of the thalamus reduces seizures. Benefit persisted for 2 years of study. Complication rates were modest. Deep brain stimulation of the anterior thalamus is useful for some people with medically refractory partial and secondarily generalized seizures.

KEY WORDS: Epilepsy, Seizures, Deep brain stimulation, Epilepsy surgery, Thalamus.

Epilepsy has a prevalence of approximately 1% in the world's population, and approximately one-third of people with epilepsy do not respond adequately to antiepileptic drugs (AEDs) (Kwan & Brodie, 2000). Electrical deep brain stimulation (DBS) via an implanted neurostimulator system is a promising therapy for epilepsy. This report documents a controlled clinical trial of stimulation of the anterior nuclei

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of thalamus for epilepsy (SANTE). The selection of the anterior nuclei (AN) as test sites was based on several factors, which include the initially positive results in the studies of Cooper (Cooper et al., 1980, 1984), three unblinded pilot trials before (Sussman et al., 1988; Hodaie et al., 2002; Kerrigan et al., 2004), and subsequently, three after (Lee et al., 2006; Lim et al., 2007; Osorio et al., 2007) the randomized study, which showed approximately 50% seizure reduction. Stimulation of the AN, which projects both to superior frontal and temporal lobe structures commonly involved in seizures, produces electroencephalography (EEG) changes (Kerrigan et al., 2004) and inhibits chemically induced seizures in laboratory models (Mirski et al., 1997).

Methods

Participants

Eligible participants were 18–65 years old, with partial seizures including secondarily generalized seizures, at least 6 per month, but no more than 10 per day, as recorded in a 3-month daily seizure diary. At least three AEDs must have failed to produce adequate seizure control prior to baseline, with one to four AEDs used at the time of study entry. Protocol exclusions included conditions that would interfere with electrode implantation or execution of the protocol; progressive neurologic or medical diseases, such as brain tumors or neurodegenerative disease; any nonepileptic seizures; IQ less than 70, inability to take neuropsychological tests or complete seizure diaries; and pregnancy. All participants granted institutional review board (IRB)–approved informed consent. Vagus nerve stimulators, if present, were removed at the time of DBS device implantations.

Study design

The trial utilized a prospective, randomized, double-blind, parallel group design. The trial was registered on January 18, 2005 at clinicaltrials.gov (NCT00101933). DBS surgery was done after a 3-month baseline with AED use remaining stable. The patient was allowed to proceed to implantation after satisfying implant inclusion and exclusion criteria (seizure frequency, stable AEDs, no elevated risks for bleeding). Implantation was with Medtronic Model 3387 DBS leads (Medtronic, Minneapolis, MN, U.S.A.), connected to a dual-channel Model 7428 Kinetra Neurostimulator (Medtronic) via Model 7482 Low Profile Extensions (Medtronic) connectors tunneled subcutaneously. DBS electrodes were implanted in the AN bilaterally using a stereotactic technique. The implantation procedure was standardized across centers with respect to equipment and targets. General anesthesia was the method of choice. Surgeons were allowed to implant with use of a frame or with a frameless system. Lead positions were verified postoperatively with magnetic resonance imaging (MRI). The most centrally located contact within each AN was selected as the site for cathodal referential stimulation with stimulator case as anode. If no electrodes were located in AN, the involved lead was removed and a new one placed.

One month after implantation, participants were randomized to stimulation at 5 V or no stimulation at 0 V (control), using 90 μs pulses, 145 pulses/s, ''ON'' 1 min, and ''OFF'' 5 min. Randomization was done by a central statistical site, using random numbers tables, a one-to-one allocation to active stimulation versus control, balanced at each study site, and with no weighting for any subject characteristics. No care or assessment personnel knew the voltage settings. Medications were kept constant during the 3-month blinded phase and the 9-month unblinded phase. The primary efficacy objective was demonstration that the monthly seizure rate was reduced from baseline in the stimulated group more than in the control group. Other outcome measures included Liverpool Seizure Severity Scale (LSSS), Quality of Life in Epilepsy (QoLIE-31), and neuropsychological testing. All adverse events were reviewed for relation to DBS therapy, systems, or procedures by a clinical events committee. An independent data and safety monitoring board (DSMB) reviewed adverse event summaries throughout the trial.

After 3 months of blinded treatment, all participants received stimulation from month 4 to month 13 in an unblinded phase. Limited stimulation parameter changes were allowed. At the end of month 13, participants entered the long-term follow-up in which AEDs and stimulation parameters could vary freely. Figure 1 shows the study design and subject flow through the protocol.

Statistical analysis methods

Major analyses were defined prospectively in the study's statistical analysis plan and protocol. The primary endpoint was a comparison of seizure reductions in the blinded phase. Analysis was conducted using a protocol-prespecified generalized estimating equations (GEE) model (Hanley et al., 2003) for repeated measures, based on a negative binomial distribution. The GEE model is conceptually similar to an analysis of variance (ANOVA) study, with repeated measures testing at sequential study visits. The prespecified factors in the GEE model included the intercept, treatment effect, log of the baseline seizure counts, baseline covariates, visit, treatment-by-visit interaction, and an offset parameter to account for the number of days in each month. Covariates and factors were considered for inclusion in the final model ($p < 0.1$) using stepwise regression. Least squares means were used to estimate adjusted treatment differences. The primary analysis required that patients be included in the analysis if at least 70 of 84 days of seizure diary data were available during the blinded phase. Additional prespecified supportive analyses included patients with at least 1 diary day (intent-to-treat), other sensitivity analyses (per-protocol, and as-treated), and prespecified and post hoc subgroup analyses of those with a previous vagus nerve stimulation (VNS) or resective surgery.

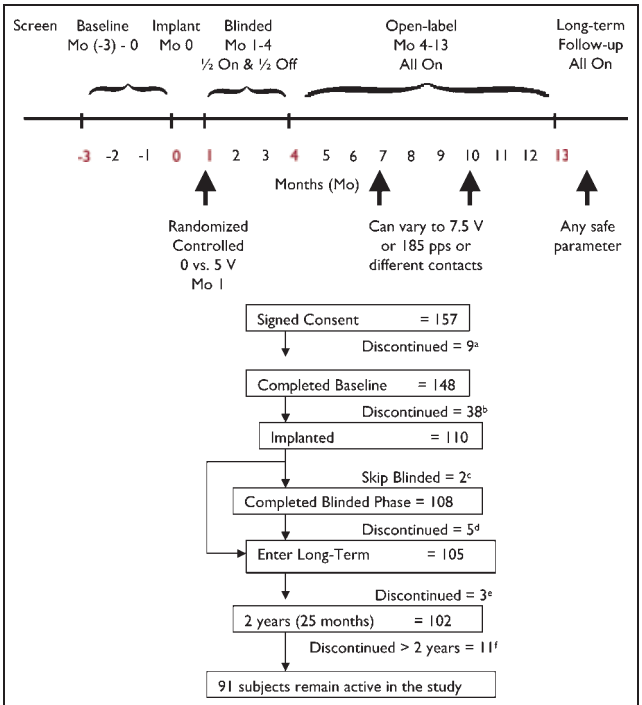

Figure 1.
Participant timeline and study entry. The number of patients that entered or discontinued at each phase is indicated in the figure. Reasons for discontinuation between phases are: [a]consent: enrollment failure (5), withdrawal of consent (4). [b]baseline: enrollment failure (19), withdrawal of consent (13), physician removed subject (2), lymphoma (1), sudden unexpected death in epilepsy (SUDEP) (1), emotionally labile (1), lost to follow-up (1). [c]Both patients developed an infection requiring explant. Following reimplantation, they went directly to the long-term follow-up. One patient was randomized and included in all analyses as randomized; one patient was not randomized. [d]open-label (unblinded): device explant (4: implant site infection in two subjects, discomfort, involuntary muscle contractions); SUDEP (1). [e]2 years: device explant (2: implant site infection, therapeutic product ineffective); drowning (1). [f]>2 years: device explant (8: therapeutic product ineffective in four subjects, implant site infection, cognitive disorder, meningitis, psychotic disorder); SUDEP (1); suicide (1); withdrawal of consent (1).

Non–GEE-model based comparisons used the Wilcoxon rank sum test and chi-square or Fisher's exact test for comparison of proportions. p-Values less than 0.05 (two-sided) were considered statistically significant; no adjustments were made for multiple comparisons.

A sample size of 102 provided 80% power to detect a 25% larger seizure reduction in the stimulated group. The design included a midstudy verification of the standard error assumption and futility assessment by an outside statistician and DSMB. The interim analysis resulted in no changes to sample size or study course.

Results

Study population

Of 157 enrolled participants at 17 U.S. Centers, 110 participants underwent bilateral electrode implantations. Randomization assigned 54 patients to stimulated and 55 to control groups, with comparable demographic and seizure history characteristics. Demographics for the entire group, as well as the stimulated and control groups are shown in Table 1. Through all phases, participants received a total of 325 subject-years of active stimulation, with mean duration of 3.0 ± 1.2 (maximum 5.0) years.

Efficacy

The study showed a significant effect of stimulation compared to control (Fig. 2 and Table 2).

One control group participant had only 66 of 70 protocol-required diary days for the primary analysis, and as prespecified in the protocol, was excluded from the primary analysis. The unadjusted median percent reduction from baseline in seizure frequency is shown graphically (Fig. 2) for each visit through the blinded phase. The GEE repeated-measures model, adjusting for log of age, also included a treatment by visit interaction during the blinded phase, so no single consistent estimate of treatment effect across the entire blinded phase was possible in the presence of this interaction. In other words, the model-estimated treatment effect separately for each of the three visits. The GEE model-estimated difference between groups in mean seizure frequencies, expressed as a percent of the mean seizure frequency in the control group is shown at the bottom of Table 2. The size of the relative difference increased over time, and became statistically significant in the final month of the blinded phase ($p = 0.0017$). The smaller estimated reduction in the stimulation group during the first month was due to a single participant who experienced 210 brief partial seizures corresponding to the 1 min on/5 min off cycle of stimulation in the 3 days after initial activation. The stimulator was turned off and the new seizures stopped immediately. Stimulation later was restored uneventfully with voltage reduced from 5 V to 4 V. The elimination of that outlier participant from analysis resulted in a larger reduction in the stimulation group versus control group during the first month, but the treatment by visit interaction remained, and the treatment difference was significant only for the third month of the blinded phase ($p = 0.0023$). When an intent-to-treat (ITT) analysis included the patient with <70 diary days and excluded the outlier described earlier, the treatment by visit interaction was not in the model, and the overall treatment effect across the entire blinded phase favored the stimulation group ($p = 0.039$). One participant, randomized to the control group, was seizure-free during the blinded phase. Other prespecified sensitivity analyses for the primary outcome measure included fitting the GEE model to subgroups of

Table 1. Baseline characteristics of the implanted participants[a]

Characteristics	Total (N = 110)	Stimulated (n = 54)	Control (n = 55)	p-Value[e]
Age (years)	36.1 ± 11.2	35.2 ± 11.1	36.8 ± 11.5	0.478
Female sex [no. (%)]	55 (50.0%)	29 (53.7%)	25 (45.5%)	0.389
Years with epilepsy (year)	22.3 ± 13.3	21.6 ± 13.3	22.9 ± 13.5	0.608
Baseline seizure counts per month (median)	19.5	18.4	20.4	0.957
Number of epilepsy medications at baseline [no. (%)]				
1	11 (10.0%)	5 (9.3%)	6 (10.9%)	0.288
2	55 (50.0%)	26 (48.1%)	28 (50.9%)	
3	41 (37.3%)	23 (42.6%)	18 (32.7%)	
4	3 (2.7%)	–	3 (5.5%)	
Prior surgical procedure for epilepsy [no. (%)]				
VNS implant	49 (44.5%)	21 (38.9%)	28 (50.9%)	0.207
Previous epilepsy surgery	27 (24.5%)	11 (20.4%)	16 (29.1%)	0.292
Unique surgical categories [no. (%)]				
Both a VNS and previous epilepsy resection	17 (15.5%)	6 (11.1%)	11 (20.0%)	0.511
Neither a VNS nor a previous epilepsy surgery	51 (46.4%)	28 (51.9%)	22 (40.0%)	
Previous epilepsy surgery only	10 (9.1%)	5 (9.3%)	5 (9.1%)	
VNS implant only	32 (29.1%)	15 (27.8%)	17 (30.9%)	
Seizure types[b] [no. (%)]				
Complex partial	102 (92.7%)	51 (94.4%)	50 (90.9%)	0.716
Partial to secondarily generalized	85 (77.3%)	38 (70.4%)	46 (83.6%)	0.100
Simple partial	74 (67.3%)	37 (68.5%)	36 (65.5%)	0.734
Generalized[c]	5 (4.5%)	3 (5.6%)	2 (3.6%)	0.679
Other	1 (0.9%)	–	1 (1.8%)	n/a
Location of seizure onset[d] [no. (%)]				
Temporal lobe	66 (60.0%)	35 (64.8%)	30 (54.5%)	0.275
Frontal lobe	30 (27.3%)	15 (27.8%)	15 (27.3%)	0.953
Diffuse or multifocal	10 (9.1%)	5 (9.3%)	5 (9.1%)	1.0
Other	10 (9.1%)	5 (9.3%)	5 (9.1%)	1.0
Parietal lobe	5 (4.5%)	2 (3.7%)	3 (5.5%)	1.0
Occipital lobe	4 (3.6%)	3 (5.6%)	1 (1.8%)	0.363

VNS, vagus nerve stimulator.

[a]Plus–minus values are means ± standard deviation (SD). One implanted subject was not randomized; therefore, the Stimulated (n = 54) and Control (N = 55) have one less patient than the total (N = 110).

[b]Participants may experience more than one seizure type.

[c]Five participants had generalized-from-onset seizures in addition to partial seizures.

[d]Participants may have seizures from more than one onset location.

[e]p-Value for comparison of stimulated and control groups.

participants without AED dose changes and including only stimulation group participants whose devices were off <5% or <20% of the time. All sensitivity analyses confirmed the significant reduction in seizure frequency in the stimulation group versus the control group by the end of the blinded phase. Changes in additional outcome measures did not show significant treatment group differences during the double-blind phase, including 50% responder rates, LSSS, or QoLIE-31 scores, although all were significantly improved compared to baseline by the end of the unblinded phase. Complex partial seizures improved more in the stimulated group versus controls over the entire blinded phase (36.3 vs. 12.1% improvement, p = 0.041, outlier removed). The seizure type prospectively designated by the participant as being ''most severe'' improved 40% in the stimulated group versus 20% in the control group (p = 0.047). As another index of seizure severity, during the blinded phase, injuries produced by seizures occurred in 26% of the control subjects and 7% of the actively stimulated subjects (p = 0.01).

Effectiveness of therapy depended upon region of seizure origin. Subjects with seizure origin in one or both temporal regions had a median seizure reduction compared to baseline of 44.2% in the stimulated group (n = 33) versus a 21.8% reduction in subjects receiving control treatment (n = 29, p = 0.025). Subjects with seizure origin in frontal, parietal, or occipital regions did not demonstrate significant differences in seizure reduction between the stimulated and control group. Subjects with multifocal or diffuse seizure origin showed a 35.0% reduction compared to a 14.1% reduction in the control group, but with only eight and nine subjects, respectively, in each group this difference did not achieve significance. Participants with prior implantation of a VNS or with prior resective epilepsy surgery showed improvements comparable to those without these prior therapies.

Unblinded and long-term follow-up

At completion of the blinded phase (month 4), 108 participants entered the unblinded phase of the trial and

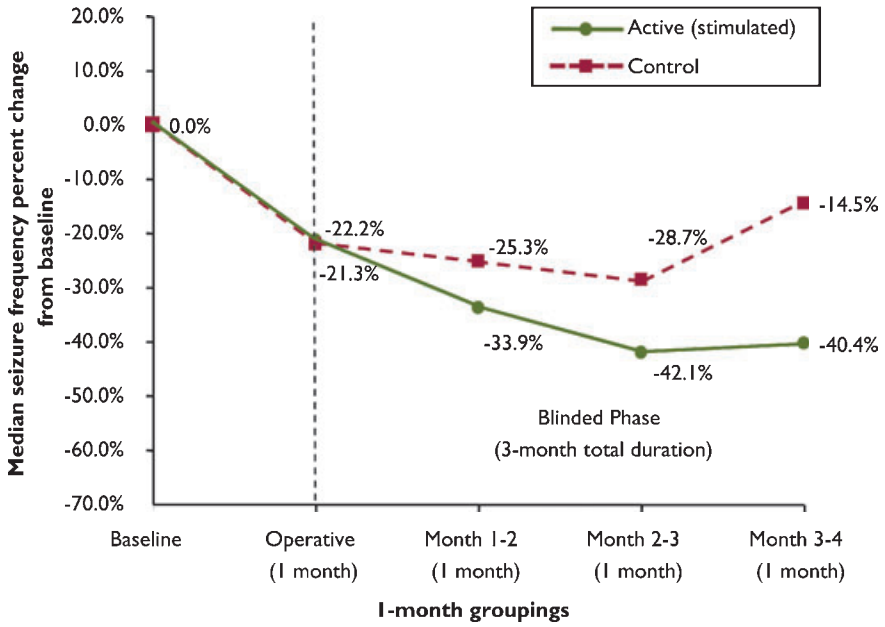

Figure 2.
Unadjusted median percent change (baseline thru blinded phase) in seizure frequency. The graph shows unadjusted median total seizure frequency percent change from baseline by 1-month groupings and treatment group during the blinded phase. Patients (n = 108) included in this graph were those with at least 70 diary days in the blinded phase (including the outlier). The operative datapoint contains cumulative data from hospital discharge to 1 month postimplantation but prior to randomization (no active stimulation). Month 1–2 contains cumulative data from month 1 visit to month 2 visit. Month 2–3 contains cumulative data from month 2 visit to month 3 visit. Month 3–4 contains cumulative data from month 3 visit to month 4 visit.

stimulation was set to 5 V, 145 pulses per second, 90 μs, 1 min on, 5 min off, in all participants. At investigator discretion, changes in voltage or frequency were allowed at month 7 and month 10, or at any time in the case of an intolerable adverse event (AE). Changing stimulation parameters to 7.5 V or 185 Hz did not reduce seizures more than initial settings, but these changes were not systematically studied.

Long-term follow-up began at 13 months with 105 participants, all receiving stimulation, adjusted at physician discretion. The median seizure frequency percent change from baseline for patients with at least 70 diary days prior to the visit was −41% (n = 99) at 13 months and −56% (n = 81) at 25 months. On an ITT basis, respective numbers are −44% (n = 108) and −57% (n = 103). The 50% responder rate was 43% (n = 99) at 13 months, 54% (n = 81) at 25 months, and 67% at 37 months (n = 42, some subjects have not yet completed 3 years). Two participants were seizure-free from months 4–13 and 14 (12.7%) were

Table 2. GEE Model adjusted mean percent difference in seizure frequency

	Month 1–2		Month 2–3		Month 3–4	
	Adjusted % difference[a]	p-value	Adjusted % difference[a]	p-value	Adjusted % difference[a]	p-value
All participants—primary analysis (active n = 54, control n = 54)	20%	0.50	−10%	0.40	−29%	0.0017
With outlier excluded (active n = 53, control n = 54)	−10%	0.37	−11%	0.34	−29%	0.0023
ITT (active n = 54, control n = 55)	19%	0.52	−10%	0.40	−29%	0.0016
ITT with outlier excluded (active n = 53, control n = 55)	−11%	0.34	−11%	0.34	−29%	0.0022
Overall estimate	−17%	0.039				

[a]Adjusted percent difference is calculated as 100% × (estimated active group mean−estimated control group mean)/(estimated control group mean) using the estimated values from the GEE model. The factors included in the final GEE model were the intercept, treatment effect, log of the baseline seizure counts, log of age, visit, treatment-by-visit interaction, and the offset .

The table shows the adjusted results from the GEE model from the primary analysis (n = 108; all patients with ≥70 diary days); primary analysis with data from one outlier patient excluded (n = 107), and the corresponding ITT analyses (n = 109, n = 108 with the outlier patient excluded). The effect of the one outlier patient is apparent with the model-adjusted values at the Month 1–2 time point. p-Values are based on a Wald test. GEE, generalized estimating equations; ITT, intent to treat.

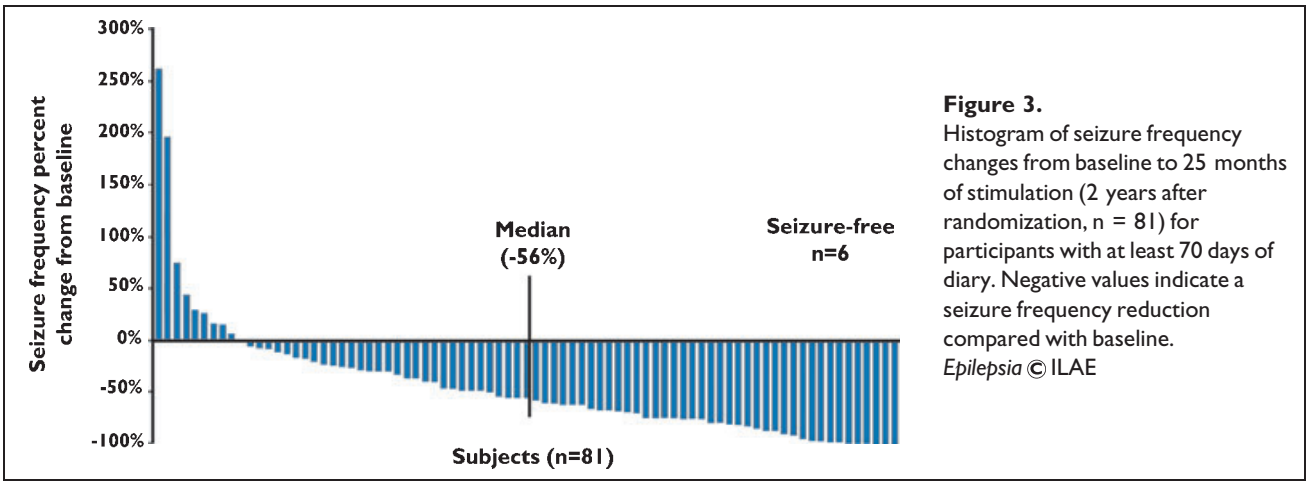

Figure 3.
Histogram of seizure frequency changes from baseline to 25 months of stimulation (2 years after randomization, n = 81) for participants with at least 70 days of diary. Negative values indicate a seizure frequency reduction compared with baseline.
Epilepsia © ILAE

seizure-free for at least 6 months. LSSS change from baseline (lower is better) was −13.4 ± 21.4 (n = 103) at 13 months and −12.4 ± 20.7 (n = 99) at 25 months ($p < 0.001$ for each). QoLIE-31 score improved from baseline by 5.0 ± 9.2 (n = 102) and 4.8 ± 9.3 (n = 98) at 13 and 25 months ($p < 0.001$ for each). For LSSS and QoLIE-31, results are reported for all subjects with both baseline and follow-up collected.

All of the AEDs commonly used in the United States were represented in list of medications taken by the study subjects. Our data do not point to any clear interaction between effectiveness of stimulation and use of a particular AED; however, the study was not powered to detect such a relationship.

Figure 3 is a histogram of seizure frequency changes for each participant using Primary Analysis methodology (at least 70 diary days during the 3 months prior to the month 25 visit). Maximum possible improvement is 100%, whereas there is no limit to possible worsening. Three patients had >50% worsening of seizures. This was due to increased numbers of simple partial seizures. Complex partial seizures were reduced in two and approximately constant in the third.

Six subjects were seizure-free for the 3-month segment at the end of 2 years of stimulation. Thirteen of 81 patients completing to 2 years (16%) had median a seizure frequency reduction of 90% or greater, compared to baseline. Fourteen patients (representing 13% of the 110 implanted patients) were seizure-free for at least 6 months during the protocol. Eight patients (7.3%) were seizure-free for at least 1 year, four (3.6%) for at least 2 years, and one (0.9%) for more than 4 years.

Adverse events

From implantation through month 13, 808 AEs were reported in 109 participants; 55 events in 40 participants were categorized as serious (usually because of required hospitalization), and 238 (29.5%) of the 808 events were considered device-related. The most common device-related AEs were paresthesias in 18.2% of participants, implant site pain in 10.9%, and implant site infection in 9.1%, all of which decreased in frequency between years 1 and 2. Leads initially implanted outside the AN in 8.2% of subjects were replaced. Eighteen participants (16.4%) withdrew from the study after the implantation because of AEs (see Fig. 1). None withdrew during the blinded phase.

Paresthesias at the stimulation site could possibly unblind the study subjects. Seven subjects had paresthesias during the blinded phase: five in the stimulation group and two in the control group. All reports of paresthesias occurred in the first month of the blinded phase. Of the five patients in the active stimulation group who experienced paresthesias, only three correctly guessed stimulation as their treatment group. Random guessing would have resulted in 2.5 patients selecting stimulation as the treatment group. Therefore, the occasional occurrence of paresthesias did not invalidate the blinding of treatment group.

Deaths

Among 110 implanted participants with a mean follow-up of 3 years, there were five deaths. No participant died during the operative month or 3-month double-blind phase. However, in the baseline phase before surgery, one participant was found dead, attributed to probable sudden unexplained death in epilepsy (SUDEP). In the long-term follow-up phase, one participant died unobserved in a bathtub (drowning), and another committed suicide, with probable relation to recent life events. One patient each in the unblinded (Pilitsis et al., 2008) and long-term follow-up phase died from SUDEP, leading to a rate of 6.2 per 1,000 years. None of the deaths were judged device-related by center investigators.

Hemorrhage

There were no symptomatic or clinically significant hemorrhages, but five hemorrhages (4.5% of participants) were detected incidentally by neuroimaging.

Table 3. Adverse events occurring in >5% of subjects in either the active or control group during the Blinded Phase, ordered by difference between groups

	Active		Control			
Preferred term	Number of subjects	% (n = 54)	Number of subjects	% (n = 55)	Difference[a]	p-value[b]
Depression	8	14.8%	1	1.8%	13.0%	0.0162[c]
Memory impairment	7	13.0%	1	1.8%	11.1%	0.0316[c]
Confusional state	4	7.4%			7.4%	0.0568
Anxiety	5	9.3%	1	1.8%	7.4%	0.1130
Paraesthesia	5	9.3%	2	3.6%	5.6%	0.2706
Influenza	3	5.6%			5.6%	0.1182
Partial seizures with secondary generalization[d]	5	9.3%	3	5.5%	3.8%	0.4890
Simple partial seizures[d]	3	5.6%	1	1.8%	3.7%	0.3634
Complex partial seizures[d]	5	9.3%	4	7.3%	2.0%	0.7420
Anticonvulsant toxicity	3	5.6%	4	7.3%	−1.7%	1.0000
Dizziness	3	5.6%	4	7.3%	−1.7%	1.0000
Headache	2	3.7%	3	5.5%	−1.8%	1.0000
Excoriation	1	1.9%	3	5.5%	−3.6%	0.6180
Contusion	1	1.9%	4	7.3%	−5.4%	0.3634
Nasopharyngitis	1	1.9%	5	9.1%	−7.2%	0.2057
Upper respiratory tract infection			4	7.3%	−7.3%	0.1182
Injury	1	1.9%	6	10.9%	−9.1%	0.1130

[a]Positive, more frequent in the active group; negative, more frequent in the control group.
[b]Fisher's exact test.
[c]Statistically significant.
[d]New or worse seizures, or seizures meeting serious adverse event criteria.

Infection

Over the entire study period, 14 participants (12.7%) developed implant site infections either in the stimulator pocket (7.3%), the tunneled lead extension tract (5.5%), or at the site of the burr hole (1.8%). Another patient had a meningeal reaction. None were parenchymal brain infections. All infections were treated with antibiotics, and nine with additional removal of hardware; three participants later had uneventful reimplantation.

Seizures and status epilepticus

Subjects were asked to record in their diary any new types of seizures. In the stimulated group during the blinded phase, two subjects reported new simple partial seizures, one reported a new complex partial seizure type, and one a new secondarily generalized seizure type. Control group subjects during the blinded phase reported one new simple partial and one new complex partial seizure type. New seizure types were reported by 7 patients in the unblinded phase and by 10 patients in the long-term follow-up phase. Overall, there were 23 new seizure types in 20 subjects: 14 represented simple partial seizures, three complex partial seizures, four partial onset, secondarily generalized seizures, and two generalized seizures with no specification of a partial onset.

Five participants (4.5%) experienced status epilepticus during the trial. Two were after implantation, but before initiation of stimulation, in patients who had missed one or more doses of their AEDs. A third participant was hospitalized for complex partial status epilepticus during month 2 of the blinded phase, with stimulation ''ON.'' A fourth participant had onset of confusion and epileptiform EEG changes when the stimulator was turned on after the blinded phase. Stimulation was stopped and the seizures resolved within 5 days. A fifth participant had tonic–clonic status epilepticus at month 49, 1 year after stimulation was discontinued.

Blinded phase adverse events

AEs from the blinded phase are shown in Table 3. Significantly more participants in the stimulated group compared to the control group reported AEs relating to depression (8 vs. 1) and memory impairment (7 vs. 1). One depression event in a stimulated patient was judged serious. Prior history of depression was identified in seven of the eight stimulation group participants, and three were on medications for depression at baseline. Depression symptoms resolved in four of the eight, over an average of 76 days (range 14–145). Four patients reporting depression had more than a 50% seizure frequency reduction at the end of the blinded phase. No memory impairment adverse event was judged serious, and all resolved over 12–476 days. In contrast to spontaneously reported complaints, neuropsychological test scores for cognition and mood did not differ between control and stimulated groups at the end of the blinded phase.

Persons with epilepsy are believed to be at a higher risk for incurring accidental injury, such as contusions, wounds, abrasions, fractures, and concussions. Considering any blinded phase events that are related to a seizure, patients in

the stimulation group experienced fewer seizure-related injuries (7.4%) than did patients in the control group (25.5%, p = 0.01).

Discussion

This study demonstrated a beneficial and sustained effect on seizure frequency of bilateral AN DBS. Benefit was clear in the final month of the blinded phase and, with exclusion of the outlier who had 210 seizures corresponding to the five-minute stimulation cycle when the stimulator was turned on, through the entire blinded phase. Improvement rates observed compare favorably with a mean 47% improvement in 28 participants participating in six small uncontrolled studies of AN stimulation (Sussman et al., 1988; Hodaie et al., 2002; Kerrigan et al., 2004; Lee et al., 2006; Lim et al., 2007; Osorio et al., 2007). By 2 years of stimulation, seizures were reduced by a median 56%, a 50%-responder rate improvement occurred in 54% of patients, seizures were less severe, and quality-of-life was improved.

Group differences likely were due to a stimulation treatment effect. Participants were unaware of their treatment group, so the difference was not due to placebo effect. Our results do not definitively rule out a contribution from a microlesion effect (Hodaie et al., 2002). However, the microlesion hypothesis cannot account for the improvement in the stimulated group versus the control group during the blinded phase, nor can a microlesion effect account for the progressive reduction in seizure frequency over time that we observed during long-term follow-up. The control group improved after month 4 with initiation of stimulation, suggesting an effect of stimulation independent of the earlier implantation surgery.

The most serious potential side effects of DBS for epilepsy are death, infection, hemorrhage, and status epilepticus. These did not materialize in higher than expected numbers. Two stimulated participants died from SUDEP, but the rate of 6.2 per 1,000 is within expected range for this study population (Dasheiff, 1991). None of the deaths were attributed by treating physicians or DSMB to lead implantation or stimulation. Our 12.7% infection rate is similar to the 9.9% seen in prospective studies of DBS for Parkinson's disease (de Bie et al., 2002; Weaver et al., 2009).

We had no symptomatic or clinically significant hemorrhages, but five (4.5% of participants) were seen with neuroimaging. Little information exists about expected rates of hemorrhage with implantations in an epilepsy population. Implantation of DBS leads into subthalamic nuclei for Parkinson's disease (Parkinson's Disease Study Group, 2001) produced hemorrhage and associated hemiparesis in three participants (3%). A study of 149 implants into thalamus or basal ganglia for movement disorders in 86 participants (Beric et al., 2001) documented clinically significant hemorrhages in two (2.3%), and a third participant had a subdural hematoma discovered 2 months after implantation. A series of 567 electrode placements for DBS, seizure recordings, or radiofrequency lesions in 259 participants (Sansur et al., 2007) resulted in symptomatic hemorrhage in 1.2%, with 0.7% having lasting symptoms.

Five participants experienced status epilepticus. One cohort study of children showed status occurring in 4.4% at 2 years, and 8.2% at 5 years (Berg et al., 2004). In our trial, occurrence of two cases of status epilepticus soon after implantation and before stimulation raises the possibility of an early postimplantation effect, in addition to effects of some patients missing medications**.** Two participants had stimulus-linked seizures upon stimulus initiation, resolving with lower voltage. Patients, therefore, should be observed carefully after initiating stimulation. With some participants stimulated every 5 min for up to 4 years, none showed ''kindling'' (Goddard et al., 1969), herein defined as the delayed emergence of seizures related to stimulation and increasing over time.

Neuropsychological test scores for cognition and mood did not differ between control and stimulated groups at the end of the blinded phase. Stimulation might nonetheless have induced or worsened depression in some individual participants. No quantitative information is available from the medical literature about effects on mood of AN stimulation. Stimulation of the subthalamic nucleus produced memory decline or psychiatric disturbance in 18.8% of participants (Hariz et al., 2008). Fisher et al. (1992) observed no change in mood with centromedian thalamic stimulation for intractable seizures. Some participants paradoxically experience depression or other psychiatric symptoms after improved seizure control (Trimble & Schmitz, 1998). Neuropsychological testing also showed no group differences on cognitive function, but memory impairment was reported by more participants in the stimulated group.

Mechanisms of action of DBS are under study, but remain little understood. When used for movement disorders, DBS invokes a mixture of excitatory and inhibitory effects, ultimately resulting in disruption of neuronal networks (Lozano & Eltahawy, 2004). In hippocampal slice model systems (Durand, 1986; Gluckman et al., 1996), high frequency stimulation causes negative slow potential shifts and increased extracellular potassium accumulation, resulting in decreased neuronal excitability. Why electrical stimulation of thalamus reduces seizures remote from the stimulation site is presently unknown. Subjects with temporal origin of seizures achieved relatively greater benefit of stimulation during the blinded phase, compared to those with seizures from other lobes or seizures multifocal in origin. Multifocal or diffuse seizures showed a trend toward benefit, but subgroup size was too small to draw conclusions. Benefit to those with temporal seizure foci may reflect participation of mesial temporal lobe along with the AN of thalamus in the limbic circuit of Papez (Papez, 1937).

Bilateral DBS of the AN reduces seizure frequency in medically refractory patients. Benefit of stimulation in this population usually was palliative, but 14 participants (12.7%) became seizure-free for at least 6 months. Improvements were seen in some participants previously not helped by multiple AEDs, VNS, or epilepsy surgery. Implantation and stimulation did not directly produce enduring serious complications in this study, but this therapy is invasive and serious complications can occur. Additional clinical experience may help to establish the best candidates and stimulation parameters, and to further refine the risk–benefit ratio of this treatment. This randomized trial shows benefit of anterior thalamic DBS in some epilepsy patients who were refractory to previous treatments.

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Disclosures

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

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