Vagus Nerve Stimulation in Patients With Alzheimer's Disease: Additional Follow-Up Results of a Pilot Study Through 1 Year

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Background: Cognitive-enhancing effects of vagus nerve stimulation (VNS) have been reported during 6 months of treatment in a pilot study of patients with Alzheimer's disease (AD). Data through 1 year of VNS (collected from June 2000 to September 2003) are now reported.

Method: All patients (N = 17) met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD. Responder rates for the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and Mini-Mental State Examination (MMSE) were measured as improvement or absence of decline from baseline. Global change, depressive symptoms, and quality of life were also assessed. Cerebrospinal fluid (CSF) levels for total tau, tau phosphorylated at Thr181 (phosphotau), and Aβ42 were measured by standardized enzyme-linked immunosorbent assay (ELISA).

Results: VNS was well tolerated. After 1 year, 7 (41.2%) of 17 patients and 12 (70.6%) of 17 patients improved or did not decline from baseline on the ADAS-cog and MMSE, respectively. Twelve of 17 patients were rated as having no change or some improvement from baseline on the Clinician Interview-Based Impression of Change (CIBIC+). No significant decline in mood, behavior, or quality of life occurred during 1 year of treatment. The median change in CSF tau at 1 year was a reduction of 4.8% (p = .057), with a 5.0% increase in phosphotau (p = .040; N = 14).

Conclusion: The results of this study support long-term tolerability of VNS among patients with AD and warrant further investigation.

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Alzheimer's disease (AD) is a devastating, progressive condition associated with memory and cognitive disturbances, mood swings and behavioral changes, and quality-of-life reductions. Estimates indicate that more than 4.5 million persons are currently affected in the United States by AD.[1] The elderly population is the fastest growing population in the United States, and the prevalence of AD is expected to nearly triple by the year 2050 in the absence of preventive treatments.[1] AD is the most common cause of dementia in persons older than 65 years, with 1 in 10 older than 65 years afflicted and half among those older than 85 years afflicted.[2] The economic burden to society is substantial. In 1991, the average lifetime cost of caring for a patient with AD was $174,000.[3] Additionally, family caregivers of patients with AD often experience lost wages, increased illness, and decreased quality of life because of the burden of caring for the patient.

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The U.S. Food and Drug Administration (FDA) had approved 5 drugs for the treatment of AD. Four of these (tacrine, donepezil, rivastigmine, and galantamine) inhibit acetylcholinesterase and received approval on the basis of cognitive and global improvements relative to placebo in controlled clinical trials.[4–8] In October 2003, the FDA approved memantine, a low affinity glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist, for the treatment of patients with moderate to severe AD as monotherapy or as combination therapy with a cholinesterase inhibitor (ChEI) on the basis of cognitive and global improvements relative to placebo.[9,10] At present, none of these treatments have been shown to modify the disease process in patients with AD, but they do provide benefit to the patient, family, and caregivers by slowing the patient's progressive decline. Antipsychotics and antidepressants also are used to treat cognitive and behavioral symptoms of the disease.

AD is pathologically characterized by the accumulation of amyloid plaques and tau-associated neurofibrillary tangles. Patients with AD have increased cerebrospinal fluid (CSF) levels of tau protein and decreased CSF levels of β-amyloid$_{1–42}$.[11–14] Although patients with AD experience significant elevations in CSF tau levels, CSF tau levels have been shown to remain stable over extended periods of time.[15–17]

Several neurotransmitter systems are pathologically altered in AD. Cholinergic neurons in the nucleus basalis of Meynert degenerate early in the course of the disease.[18] These neurons provide widespread projections to the association cortices, and loss of acetylcholine is the mechanistic basis for cholinesterase inhibition in AD. Glutamatergic function also is dysregulated in AD, with inhibition of the pathological stimulation of the NMDA receptor providing the scientific rationale for the mechanism of the noncompetitive glutamate antagonist, memantine. In addition to the atrophy of the basal forebrain cholinergic system, marked neuronal loss occurs within the locus ceruleus and the raphe nucleus in AD.[19] Significant reductions of norepinephrine in the temporal cortex occur in AD and correlate with the degree of cognitive impairment.[20] Disturbances in serotonin metabolism also have been reported in AD.[21]

Vagus nerve stimulation (VNS) has been shown to activate the locus ceruleus[22] and to increase norepinephrine output into the basolateral amygdala[23] and hippocampus[23] in animal models. Activation of the raphe nucleus with VNS also has been recently demonstrated.[24] Recruitment of serotonergic and noradrenergic pathways via VNS may confer additional benefit to the already established treatment modalities for AD by facilitating alternative or complementary cognitive and behavioral pathways.

We have previously reported cognitive-enhancing effects of VNS during the first 6 months of treatment in a small pilot study of 10 patients with AD.[25] In this follow-up report, we include an additional 7 patients, with follow-up available for at least 1 year for all 17 patients. These data extend the observations of the first publication to a slightly larger sample size and provide safety information and observational outcome data for an extended duration of treatment.

METHOD

The VNS and AD study methods have been previously described in detail.[25] In brief, patients diagnosed with AD[26] and aged 40 to 80 years were evaluated. At study entry, patients had to have a Mini-Mental State Examination (MMSE) score of 16 to 24. Patients were excluded from the study if they had clinically unspecified dementia, mixed dementia, a history of severe psychiatric disease, chronic alcoholism, distinct nondegenerative neurologic disease, a history of severe head injury, severe infections in the central nervous system, systemic diseases, or secondary causes of dementia.[27,28] All study patients underwent thorough clinical evaluations in accordance with a Swedish consensus that complies with international standards and with the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD.[29] The study, conducted from June 2000 to September 2003, was approved by the Ethics Committee of Göteborg University (Göteborg, Sweden) and conducted in accordance with the provisions of the Helsinki Declaration. Patients and their nearest relatives provided informed consent for study participation.

Study Overview

VNS therapy (Cyberonics, Inc; Houston, Texas) was administered using previously described methods and parameter settings.[25,30,31] All patients followed the same treatment schedule. Following implantation was a 2-week single-blind recovery period of no stimulation followed by a 2-week stimulation adjustment period during which the output current (mA) was gradually increased. After 2 weeks of treatment with VNS (4 weeks after implantation), stimulation parameters were set and remained unchanged for the remaining 8 weeks of the acute study phase. After completion of the acute phase (12 weeks total), patients were allowed to continue in the long-term follow-up phase irrespective of acute treatment outcome. During the long-term follow-up phase, clinically indicated changes to the stimulation parameters were allowed.

Concomitant Therapy

Patients on a stable regimen of ChEIs for at least 8 weeks before study entry were allowed to continue ChEI treatment. Behavioral symptoms associated with AD could be treated with antidepressants and neuroleptics;

Table 1. Baseline and Clinical Demographic Characteristics (N = 17)[a]

Characteristic	Value
Gender, male:female, N:N	6:11
Age at implant of VNS device, y	63 (57–81)
Weight, mean ± SD, kg	69.6 ± 11.3
MMSE score	21 (17–24)
ADAS-cog score	19 (7–30)
Duration of cholinergic treatment, wk	45 (16–158)
Cholinergic medications, N	
Donepezil	5
Galantamine	2
Rivastigmine	3

[a]Values are presented as median (range) unless otherwise indicated.
Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale, MMSE = Mini-Mental State Examination, VNS = Vagus Nerve Stimulation.

short-term treatment with tranquilizers, such as short-acting benzodiazepines, also was allowed. Cognition-enhancing or experimental drugs were proscribed. Previous enrollment in concomitant clinical trials or in clinical trials with cognition-enhancing drugs or antidementia drugs was not allowed. After completion of the acute phase of the study, all patients who were not initially on ChEI therapy were allowed such treatment because of the possible additive effect of VNS and cholinergic treatment on AD.

Outcome Evaluations and Measurements

The baseline medical assessments included medical history; physical, psychiatric, and neurologic examinations; laboratory blood tests; lumbar puncture; electocardiogram; and a new brain scan (CT or MRI) if more than 6 months had elapsed since the last one. The physical and neurologic examinations and the lumbar puncture were readministered at the exit of the acute phase (3 months) and at 1 year. Assessments were administered at baseline, during the recovery period, at the end of the acute phase, at 6 months, and at 1 year. The primary efficacy endpoint was the proportion of patients responding to treatment with VNS as measured by using the median change in the Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog)[32] and MMSE[33] scores from baseline. Responder rates for the ADAS-cog and MMSE were measured as improvement or absence of decline. Responder rates were evaluated separately for the ADAS-cog and MMSE by independent raters. Secondary efficacy parameters were measured by using the median changes in the Montgomery-Asberg Depression Rating Scale (MADRS)[34] and Inventory of Depressive Symptomatology–Self-Report (IDS-SR)[35] scores for the affective variables and by using the median changes in Gottfries-Brane-Steen scale (GBS)[36] scores for the behavioral variables. Quality of life was measured by the Medical Outcome Survey (MOS) 36-Item Short-Form Health Survey (SF-36),[37] and patient status was assessed by the Clinician Interview-Based Impression of Change with Caregiver Input (CIBIC+).[38] All adverse events were recorded. Because of non-normal distribution of the data, nonparametric descriptive measures were used for the analyses. The data are presented as medians rather than means because of the small number of study patients and to better account for outliers.

Cerebrospinal Fluid

Lumbar puncture was performed at baseline assessment and at 3 and 12 months of treatment. Lumbar puncture was performed at the L3/L4 or L4/L5 interspace. The first 12 mL of CSF was collected in polypropylene tubes and gently mixed to avoid gradient effects.[39] At the same time, a serum sample was taken. All CSF samples with more than 500 erythrocytes per μL were excluded. The CSF and serum samples were centrifuged at $2000 \times g$ for 10 minutes to eliminate cells and other insoluble material. Aliquots were then stored at –80°C until biochemical analysis. Quantitative determination of serum and CSF albumin was performed by nephelometry using the Behring Nephelometer Analyzer (Behringwerke AG, Marburg, Germany). The albumin ratio was calculated as [CSF albumin (mg/L)/serum albumin (g/L)] and was used as the measure of blood-brain barrier (BBB) function.[40]

CSF tau was determined by using a sandwich enzyme-linked immunosorbent assay (ELISA; Innotest hTAU-Ag, Innogenetics; Ghent, Belgium) constructed to measure total tau (both normal and phosphorylated) as described previously in detail.[41] The phosphotau (P-Thr181) ELISA was essentially designed as the Innotest hTau antigen ELISA by using the same reagents. In short, monoclonal antibody (MAb) HT7, which recognizes both normal tau and phosphotau, was used as capturing antibody, and biotinylated MAb AT270 (specific to P-Thr181 phosphotau) was used as detection antibody.[42] CSF-Aβ42 was determined using a sandwich ELISA [Innotest β-amyloid(1–42), Innogenetics; Ghent, Belgium] constructed specifically to measure β-amyloid1–42 as previously described.[43]

RESULTS

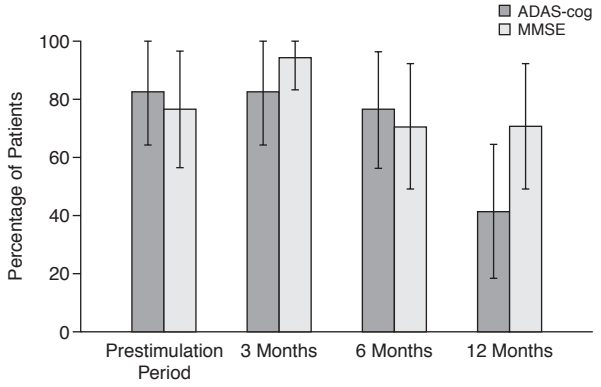
Study Patients

Of the initial 17 patients enrolled in the study, all 17 underwent implantation of the VNS device, completed the acute study, and had at least 1 year of treatment follow-up from the date of implantation. All 17 patients remained implanted and actively treated with VNS therapy beyond 1 year. The demographics and clinical characteristics of these participants are summarized in Table 1.

Safety Profile

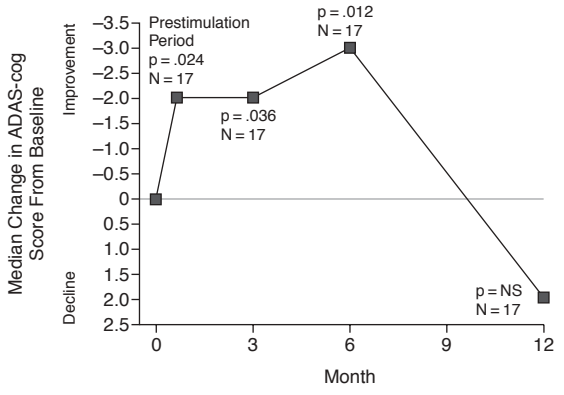
In general, VNS therapy was well tolerated. Throughout the study, the most common side effect was voice

Figure 1. Proportion of Patients Having Improvement or No Decline, Measured by the ADAS-cog and MMSE, From the Baseline Assessment to the Assessment During the Prestimulation Period and After 3, 6, and 12 Months of Treatment (N = 17 for all time points)[a]



[a]Bars indicate 95% CI.
Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale, MMSE = Mini-Mental State Examination.

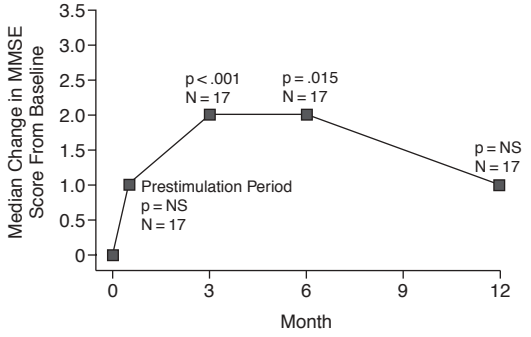
Figure 2. Median Changes in ADAS-cog Scores From the Baseline Visit Assessment to the Assessment During the Prestimulation Period and After 3, 6, and 12 Months of Treatment



Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale, NS = nonsignificant.

alteration or hoarseness (N = 16), which was reported as mild (N = 14) or moderate (N = 2) in severity. Other adverse events considered possibly, probably, or definitely related to implantation or stimulation and occurring in more than 2 patients were increased cough (N = 3), pain (N = 8), and dysphagia (N = 3). All adverse events were reported as mild or moderate, and none required discontinuation of VNS therapy or device explantation. At 12 months, coughing was no longer being reported, and reports of all other side effects also were reduced. Three patients experienced serious adverse events during the study. Two were considered unrelated to treatment, with 1 case of anxiety considered possibly related to stimulation. All study patients chose to continue with VNS therapy after 1 year of treatment.

Figure 3. Median Changes in MMSE Scores From the Baseline Visit Assessment to the Assessment During the Prestimulation Period and After 3, 6, and 12 Months of Treatment



Abbreviation: MMSE = Mini-Mental State Examination.

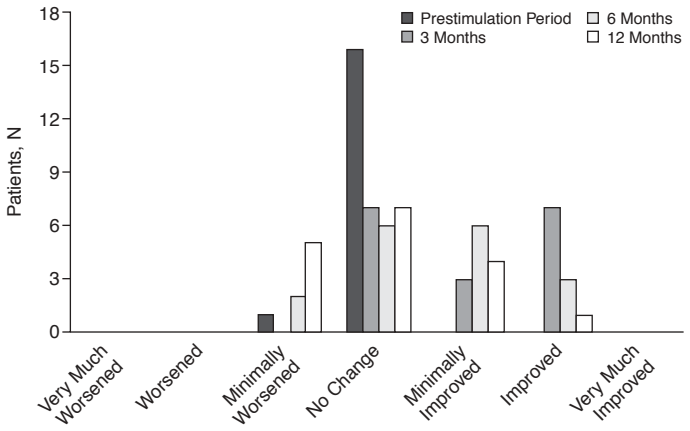
Cognitive and Global Variables

The proportion of patients having improvement or no decline at each of the assessment periods is given in Figure 1. At 6 months, 76.5% (13/17) and 70.6% (12/17) of patients showed improvement or no decline on the ADAS-cog (95% CI = 56.3% to 96.6%) and MMSE (95% CI = 48.9% to 92.3%), respectively. After 1 year of treatment, 41.2% (7/17) of patients had improvement or no decline from baseline on the ADAS-cog (95% CI = 17.8% to 64.6%), and 70.6% (12/17) of patients had improvement or no decline from baseline on the MMSE (95% CI = 48.9% to 92.3%). All 7 ADAS-cog responders at 1 year were also MMSE responders at 1 year. Six of the seven 1-year ADAS-cog responders were also responders on both the MMSE and ADAS-cog at 6 months.

Median changes from baseline in ADAS-cog and MMSE scores are shown in Figures 2 and 3, respectively. Significant improvement from baseline was observed at 3 months for both the ADAS-cog (median improvement of 2 points, $p = .036$) and MMSE (median improvement of 2 points, $p < .001$). Significant improvement was sustained at 6 months for the ADAS-cog (median improvement of 3 points, $p = .012$) and MMSE (median improvement of 2 points, $p = .015$). For both the ADAS-cog and MMSE, improvement from baseline was greater at 6 months than during the prestimulation period. Change from baseline was not significant for the ADAS or MMSE at 1 year. The median decline for the ADAS-cog at 1 year was 2 points. The median change on the MMSE at 1 year was a 1-point improvement from baseline.

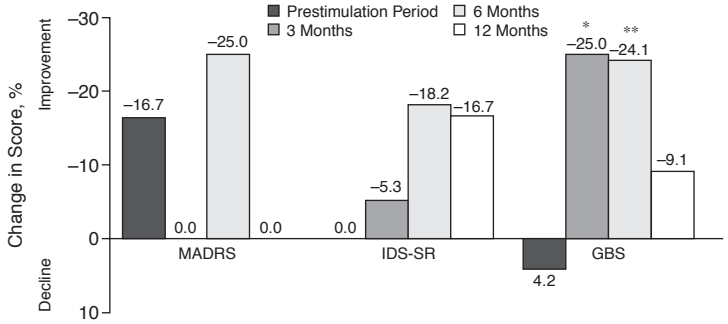
Changes from baseline according to the global impression of change as measured by the CIBIC+ are shown in

Figure 4. Distribution of Patients Showing Improvement, No Change, or Worsening of the Global Impression of Change Relative to Baseline as Scored by the CIBIC+ During the Prestimulation Period and After 3, 6, and 12 Months of Treatment With VNS (N = 17)



Abbreviations: CIBIC+ = Clinical Interview-Based Impression of Change With Caregiver Input, VNS = vagus nerve stimulation.

Figure 5. Median Percent Changes in MADRS, IDS-SR, and GBS Scores From the Baseline Visit Assessment to the Assessment During the Prestimulation Period and After 3, 6, and 12 Months of Treatment (N = 17)



*p = .021.
**p = .058.
Abbreviations: GBS = Gottfries-Brane-Steen scale, IDS-SR = Inventory for Depressive Symptomatology–Self-Report, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 4. Despite improvements on the cognitive assessments during the prestimulation surgical recovery period, 16 of the 17 patients were rated as having no change from baseline, and 1 patient was minimally worsened. At 1 year, only 5 patients were considered minimally worse than baseline with no patients rated as worsened or much worsened. Five patients were minimally improved or improved, and 7 had no change from baseline.

Mood, Comprehensive, and Quality-of-Life Variables

No significant decline in mood was seen over the 1-year study period. The median percent changes in MADRS, IDS-SR, and GBS scores are shown in Figure 5. The median MADRS score was 3 (range, 0–12; maximum score = 60) at baseline, 2 (range, 0–8) at 3 months, and 3 at 6 months (range, 0–6) and 12 months (range, 0–9). The differences in median scores between the baseline and the endpoint ratings were not significant at any time point for the MADRS. The median IDS-SR score at baseline was 13 (range, 1 to 33; maximum score = 84). No significant changes in either the MADRS or IDS-SR scores were seen between the ratings during the recovery period and the baseline ratings, indicating the absence of a placebo or practice effect for these assessments.

The median GBS score was 16 (range, 7–30; maximum score = 162) at baseline, 12 (range, 5–31) at 3 months, 11 (range, 5–41) at 6 months, and 13 (range, 3–45) at 12 months. A significant improvement of 25% was observed at 3 months ($p = .021$), and the 24% improvement at 6 months neared significance ($p = .058$) compared with baseline. The median GBS improvement at 1 year was not significant. The median GBS score during the prestimulation recovery period was 17, and the median change from baseline was a 4% worsening, indicating the absence of a placebo or practice effect on the GBS. Quality-of-life measures were relatively stable over 1 year. Median percent changes from baseline for the SF-36 subscales were less than 6% and were not significant at 3, 6, or 12 months.

Biomarkers

Baseline values of CSF tau were consistent with those previously published for patients with mild to moderate AD.[11] All patients had baseline CSF tau levels exceeding 195 pg/mL. The median value of CSF tau at baseline was 714 pg/mL (range, 202 to 1030 pg/mL). The median level of CSF β-amyloid$_{1–42}$ at baseline was 428 pg/mL (range, 299 to 764 pg/mL). Six of the 17 patients did not have CSF β-amyloid$_{1–42}$ levels below 444 pg/mL, which is less than the 92% sensitivity of this cutoff point previously reported.[11] Changes in CSF tau were not significant at 3 months. After 12 months of VNS, a slight reduction in CSF tau was observed that neared significance (median percent change of 4.8%, $p = .057$, $N = 17$). Changes in Aβ42 were not significant at 3 months or at 1 year. The median value of phosphotau at baseline was

99.5 ng/L (range, 34 to 154). After 12 months of VNS, a slight but significant increase in phosphotau was detected (median percent change of 5.0%, p = .040, N = 14). A trend for increased phosphotau also was observed at 3 months (median increase of 7.3%, p = .079, N = 14).

Concomitant Therapy

No patients took memantine during the first 12 months of VNS. Ten of the patients were taking ChEIs at the start of the study. All patients taking ChEIs at baseline had been stable on these medications for at least 3 months, with 7 of 10 taking ChEIs for 6 months or longer. The median duration of treatment with ChEIs was 45 weeks before the baseline visit (range, 16 to 158 weeks). Fourteen of the 17 patients completed 1 year of VNS therapy without any additions or changes of cognitive-enhancing medications. Two patients initiated ChEI treatment after 6 months of VNS, and 1 had a dose increase after 6 months. Of these 3 patients who initiated or increased ChEI treatment during the study, none had a response at 12 months (i.e., all 3 patients had declined from baseline) on the ADAS-cog; on the MMSE, 1 patient was stable and 2 showed a decline.

DISCUSSION

The results from this pilot provide preliminary observations of VNS as a nonpharmacologic treatment option for patients with AD. Most patients showed an improvement or no decline in cognitive function (MMSE), and 7 patients improved or showed no decline on the ADAS-cog after 1 year of VNS therapy. No patients were rated as worsened or much worsened in terms of the global impression. No significant decline in mood was seen, and quality-of-life measures remained relatively stable over the 1-year study period. VNS was well tolerated in this sample. A trend for reduction in CSF tau and a slight but significant increase in phosphotau were observed after 1 year of VNS.

The results of this study are consistent with results of other treatments for AD in that patients demonstrate an early cognitive improvement with the treatment, followed by gradual decline and a delay of decline past the baseline performance. Most of the clinical studies conducted among patients with AD have used a control group for comparison, with improvement described as the difference between active treatment and placebo. In this open-label pilot study, one is unable to ascertain how the patients would have fared had they not received VNS therapy. The absence of a control group and the small number of patients are the major limitations of this study. However, given the initial invasiveness of the surgical procedure for implantation of the VNS therapy device and the vulnerability of the patient population, an open-label pilot study in which all patients receive active treatment was warranted to establish potential benefit before randomization of patients to an inactive control. The results of this pilot study provide adequate preliminary efficacy data, together with safety and tolerability data, to justify additional studies of VNS in patients with AD. Furthermore, the sustained improvement seen on the ADAS-cog argues against a placebo effect, which is generally short-term in nature.

Despite its limitations, several interesting observations can be drawn from this study. First, no patients withdrew from the study during the first year of treatment, and all patients continued to receive stimulation treatment beyond 1 year. Although treatment with VNS therapy does require surgical implantation, long-term tolerability and lack of drug interactions may provide an additional benefit of this treatment among patients already pharmacologically burdened. Second, despite the absence of a comparator group, improvement on the MMSE was observed through 1 year with patients serving as their own controls. Without a control, it is difficult to conclude that the improvement is attributable to the treatment. It is important to note, however, that these were outpatients with no scheduled study visits between the 3-, 6-, and 12-month evaluation visits, thereby reducing the possibility of beneficial effects owing to frequent study visits.

Another important observation is the cognitive and global improvement that occurred in patients taking versus those not taking ChEIs. Given the duration of ChEI treatment before study participation for most of the study patients and the progressive decline following initial improvement with ChEIs, it is unlikely that any improvement from baseline observed in this study could be attributable to concomitant ChEI treatment. Memantine, an NMDA-receptor antagonist, received marketing approval in the United States in 2003 for both monotherapy and combination therapy, highlighting the ability of treatment interventions targeting distinct neurotransmitter systems to provide benefit to persons with AD independently or in combination.

Persons with AD often have behavior and mood disturbances that emerge or worsen as the disease progresses. Changes in mood and behavior are often more troubling to the caregiver than cognitive changes. Baseline impairments in mood and behavior were not substantial in this patient population, but showed a slight degree of improvement (results not significant) rather than worsening. Improvements on the GBS, which is a comprehensive assessment including measures of intellect, emotion, behavior, and function, were also observed at 3, 6, and 12 months of VNS and were significant at 3 months (with a trend toward significance at 6 months).

The results regarding the CSF levels of total-tau, phosphotau, and Aβ42 are difficult to interpret. A decrease in CSF total-tau after 1 year of VNS therapy in patients with AD may suggest that the ongoing axonal and

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synaptic degeneration that occurs in AD is alleviated (i.e., a normalization is occurring). However, this finding is contradicted by the increase in CSF phosphotau over 1 year, which in turn may reflect an increasing phosphorylation of tau (i.e., the pathophysiologic disease process of AD is tuned up). It may be that axonal degeneration is in fact lessened by VNS but that it does not affect the phosphorylative process of AD. However, as the power of this study is low, conclusions should be drawn with caution.

In addition to the 17 study patients whose outcome data are presented here, 4 patients were subsequently enrolled under this study protocol at Malmö University Hospital as part of an add-on study to investigate potential mechanisms of action of VNS among patients with AD. These 4 patients underwent regional cerebral blood flow (rCBF) measurements while performing a task of cognitive processing speed (AQT; Harcourt Assessment Inc, San Antonio, Tex., 2004) at baseline (before implantation) and at 3 months to evaluate changes in rCBF. Two-dimensional rCBF measurements were performed with a 64-channel system using Xe-133 as tracer as previously described.[44] The AQT[45] was used because it is a test of cognitive processing speed with an objective outcome measure and is well tolerated by demented patients during the rCBF scan. The AQT measures the time (in seconds) it takes to name 40 visually presented color-form combinations (e.g., red circle, blue line, yellow square). The test-retest stability is 0.93.[45] Among healthy patients, this task typically shows a significant and robust activation of posterior temporal, parietal, and occipital areas bilaterally, whereas frontal areas show flow decreases compared with baseline resting.[45] Patients with AD, on the other hand, consistently show an abnormal rCBF response to the task, with decreased parietal blood flow and increased frontal levels.

In 2 of the 4 patients, a clear improvement of activation was seen after 3 months of VNS compared with the baseline assessment (data not shown). Regional cerebral blood flow values were higher (4% to 8%) in temporal and temporal-parietal areas after VNS compared with baseline, whereas frontal values were lower after VNS (about 4%). This pattern of normalization of the rCBF after 3 months of VNS therapy was similar in both patients. The remaining 2 patients showed no improvement but also were not worsened in their rCBF.

The improvements described herein remain to be tested in a randomized trial, but the design for such a study presents several interesting challenges. The typical duration for an AD treatment study is 24 weeks.[46] This duration provides the appropriate balance between the length of time needed to observe an adequate treatment effect and ethical considerations about withholding treatments in the control group.

To conduct a double-blind study of an implantable device, subjects randomized to the control group would need to undergo implantation of the device but not receive treatment during the analysis period, as was the case in the study of VNS for the treatment of depression.[47] To maintain the blind, subjects would need to be seen for sham adjustments at the same frequency intervals as the active subjects. Programming and rating functions would have to be assigned to separate members of the study team and stimulation would need to be deactivated during the blinded visits with the rating clinicians. Side effects of VNS such as those reported on in this pilot study, particularly the fact that 16 of the 17 patients reported hoarseness or voice alteration with stimulation, albeit mild in most cases, still could compromise the integrity of the blind.

Alternatively, a high verses low stimulation study design could be employed, as was done for studies of VNS in the treatment of epilepsy.[48] It is important to note, however, that it has not yet been established what stimulation parameters would be nontherapeutic in AD, and voice alteration and other side effects vary with the stimulation parameters.

Importantly, because of the nature of the illness and the widespread use of both ChEIs and memantine for the treatment of AD, subjects would need to be allowed concomitant therapy. To minimize confounding factors in analyzing the data, concomitant therapy should be stable prior to entering the study and during the study period. A cost-effectiveness analysis of VNS treatment conducted in conjunction with or as a separate study also would be valuable. The long-term reductions in costs associated with caregiver burden, hospitalization or nursing home placement, and medication interventions would need to be compared with the up-front costs for the device and surgery.

Despite the difficulties inherent in a randomized study of VNS for the treatment of AD, the results of this pilot study warrant further investigation. Moderate improvements in cognitive function, as compared with baseline, were observed at 6 months of treatment, and VNS was well tolerated over 1 year of therapy. Moreover, quality of life remained stable throughout 1 year of treatment, and no patients elected to have the device deactivated or explanted.

Drug names: donepezil (Aricept), galantamine (Razadyne), memantine (Namenda), rivastigmine (Exelon), tacrine (Cognex).

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