Cognition-Enhancing Effect of Vagus Nerve Stimulation in Patients With Alzheimer's Disease: A Pilot Study

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***Background*:** Vagus nerve stimulation (VNS) is an established treatment method for therapy-refractory epilepsy and, in Europe, for treatment-resistant depression also. Clinical and experimental investigations have also shown positive effects of VNS on cognition in epilepsy and depression. The purpose of the present pilot study was to investigate the effect of VNS on cognition in patients with Alzheimer's disease.

***Method*:** All the included patients (N = 10) met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for the diagnosis of Alzheimer's disease. Before the implantation of the vagus stimulator (NeuroCybernetic Prosthesis), the patients underwent neuropsychological tests (e.g., Alzheimer's Disease Assessment Scale-cognitive subscale [ADAS-cog] and Mini-Mental State Examination [MMSE]), computerized tomography of the brain, medical/neurologic and psychological examinations (status evaluation), and lumbar puncture with investigation of the cerebrospinal fluid. The presence of depressive symptoms was rated using the Montgomery-Asberg Depression Rating Scale. The VNS was initiated 2 weeks after the implantation, and the patients were followed up with regular investigations and tests over 6 months. Response was defined as improvement or absence of impairment in ADAS-cog and MMSE scores after 3 and 6 months.

***Results*:** After 3 months of treatment, 7 of 10 patients were responders according to the ADAS-cog (median improvement of 3.0 points), and 9 of 10 patients were responders according to the MMSE (median improvement of 1.5 points). After 6 months of treatment, 7 patients were responders on the ADAS-cog (median improvement of 2.5 points), and 7 patients were responders on the MMSE (median improvement of 2.5 points). VNS was well tolerated, and its side effects were mild and transient.

Conclusion: The results of this open-label pilot study suggest a positive effect of VNS on cognition in patients with Alzheimer's disease. Further studies are warranted.

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Alzheimer's disease is a major health threat. Estimates indicate that approximately 4 million people in the United States suffer from Alzheimer's disease.[1] The prevalence of Alzheimer's disease in Sweden has been estimated to be about 150,000, with the disease affecting men and women equally.[2] Alzheimer's disease is characterized by a progressive deterioration of cognitive functions, especially memory. Other cognitive functions, for instance, visuospatial functions, language abilities, and executive functions, are also affected. Associated symptoms are mood and behavioral changes. The prognosis is poor, with no cure available. The cause of Alzheimer's disease is unknown in most cases, but mutations in a few underlying genes have been identified in familial Alzheimer's disease.[3] Symptomatic treatment aimed at enhancing cognitive functions is available in the form of acetylcholinesterase inhibitors (ChEI).[4] In most cases, these drugs have a statistically significant effect, but their effect size is limited to modest and transient improvements.[5] They seem to have a positive effect on cognition in about 50% of Alzheimer's disease patients.[6,7] With an increasing average length of life, the problem of Alzheimer's disease is escalating, and the need for alternative remedies has become urgent.

The use of vagus nerve stimulation (VNS) to modulate activity in the limbic system and higher cortex has a long history. That VNS elicits cortical activation in the frontal lobes of cats was reported already in 1938.[8] This finding has been confirmed by several other investigators.[9–11] In the 1980s and 1990s, the anticonvulsant action of VNS was demonstrated.[12–14] Since 1994 in Europe and since 1997 in the United States, VNS has been a commercially available

treatment for therapy-resistant, partial-onset epileptic seizures and, in Europe, also for generalized epileptic seizures.

Results from clinical and animal studies have shown that VNS has a positive effect on cognition. Initial case studies reported that VNS seemed to improve learning and memory.[15] These initial reports gained support from clinical studies of patients with epilepsy in whom improvements were seen in cognitive functions in general.[16] While decreased antiepileptic drug usage and seizure reduction in epilepsy patients treated with VNS quite likely contributes to overall cognitive improvement, studies in rats and humans have also shown a direct effect of VNS on memory storage. Stimulation of vagal afferents in rats immediately following an inhibitory avoidance task significantly enhanced retention performance.[17] Since the stimulation was administered following the learning task (during memory consolidation), the result cannot be attributed to a nonspecific alerting effect related to sensory perception of stimulation. Similar experiments performed in patients with epilepsy demonstrated enhanced word recognition performance when vagal stimulation is administered in conjunction with a verbal word recall task.[18] Since the test was administered 1 hour after initiation of VNS treatment, confounding variables of VNS treatment such as decreased seizures and antiepileptic drug usage were removed.

A positive effect of VNS on both cognition and mood was observed in an open-label pilot study of 60 patients with long-standing, treatment-resistant major depressive disorders (unipolar and bipolar).[19] Neurocognitive testing in 27 of these patients demonstrated improvements in motor speed, psychomotor function, language, and executive functions following 10 weeks of VNS treatment.[20] While cognitive improvement on some measures did correlate with clinical improvement of depressive symptoms in these patients, the effects of VNS on memory retention in rats and humans support a direct effect of VNS on cognition.

Indirect evidence suggests that VNS may affect local release or metabolism of neurotransmitters[21–23] that are known to be changed in Alzheimer's disease.[24–26] Furthermore, VNS has been found to modulate functional activity in widespread cortical and subcortical brain regions.[27] In patients with Alzheimer's disease, these regions are generally degenerated, and cerebral blood flow is often decreased.[28,29]

The positive effect of VNS on cognitive functions and mood in certain disorders, its stimulating effect on neurotransmitter systems that are dysfunctional in Alzheimer's disease, and its enhancing effect on cortical and subcortical metabolic functions provide a rationale for investigating VNS treatment in patients with Alzheimer's disease. The primary objective of this pilot study was to ascertain whether VNS has a cognition-enhancing effect on patients with Alzheimer's disease. Other objectives were to investigate its effects on mood and quality of life and its safety and tolerability in patients with Alzheimer's disease.

Table 1. Clinical Characteristics of 10 Patients With Alzheimer's Disease[a]

Characteristic	Value
Gender, male:female, N:N	2:8
Age, y	67.0 ± 7.6
Age at onset of dementia, y	63.5 ± 7.9
Duration of dementia, y	2.9 ± 1.4
ADAS-cog score	21.9 ± 7.0
MMSE score	21.0 ± 2.4

[a]Values are mean ± SD unless otherwise indicated. Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale, MMSE = Mini-Mental State Examination.

METHOD

Subjects

The study included 10 patients with a diagnosis of probable Alzheimer's disease, as defined in the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[30] The patients had been admitted to the neuropsychiatric diagnostic unit at the Institute of Clinical Neuroscience, Sahlgrenska University Hospital, Mölndal, Sweden, for clinical evaluation of dementia. To enter the study, patients had to be between 40 and 80 years of age and to have a Mini-Mental State Examination (MMSE) score of 16 and 24 at the time of inclusion. Excluded were patients with clinically unspecified dementia, patients with mixed dementia (e.g., concomitant Alzheimer's disease and vascular dementia), and those with a history of severe psychiatric disease (e.g., schizophrenia, major depressive disorder), chronic alcoholism, distinct nondegenerative neurologic disease (e.g., normotensive hydrocephalus). Furthermore, those with a history of severe head injury, severe infections in the central nervous system, systemic diseases (e.g., malignant tumors), or secondary causes of dementia (e.g., hypothyroidism), as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[31] or the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10),[32] were also excluded.

The patients' ages at enrollment ranged from 57 to 78 years and the duration of Alzheimer's disease from 1.5 to 6 years. The median MMSE score at baseline was 21 (range, 16–24). Two patients had hypertension, 1 had hypothyroidism (without relation to the development of Alzheimer's disease), 1 had allergy, 1 had a history of repeated headaches, and 1 had neck pain (neuralgia). One patient had experienced 2 episodes of epileptic seizures 30 years before being included in the study. She had had no treatment for epilepsy for over 15 years. The patients' demographics are summarized in Table 1.

All the patients underwent a thorough clinical evaluation, including medical history; physical, neurologic, and psychiatric examinations; screening laboratory tests

of blood; routine analysis of the cerebrospinal fluid (CSF); electrocardiography (ECG); chest x-ray; electroencephalography; and computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain. Clinical evaluations and diagnosis were made in accordance with a Swedish consensus that complies with international standards and with the NINCDS-ADRDA criteria for Alzheimer's disease.[33]

The Ethics Committee of Göteborg University approved the study. All the patients and their nearest relatives gave their informed consent for participation in the study, which was conducted in accordance with the provisions of the Helsinki Declaration.

Treatment Overview

VNS was effected with the NeuroCybernetic Prosthesis (NCP) system (Cyberonics Inc., Houston, Tex.). This system and the implantation technique were identical to those used in studies on treatment-resistant depression[19] and in the treatment of epilepsy.[16] The NCP system includes an implantable and multiprogrammable pulse generator that delivers electrical signals to the left vagus nerve (the tenth cranial nerve) via a bipolar lead. The pulse generator is programmed via a programming wand attached to a computer, which sets or adjusts stimulation parameters. The stimulation parameters used in this study were within the range of the parameters used in previous studies and in commercially available treatment of epilepsy. The initial stimulation parameters were 0.25 mA, 20 Hz, and 500 μsec, with stimulation on for 30 seconds followed by a pause in stimulation for 5 minutes. Over a 2-week stimulation adjustment period, the stimulation level was increased in 0.25-mA increments and then fixed for the remaining 8 weeks of the first phase of the study. A decrease in stimulation parameters was permitted if intolerable side effects occurred. More detailed information about the NCP system is available in the literature.[34]

Study Overview

All the patients followed the same treatment schedule. After they had given their consent for participation in the study, baseline assessments were performed within 6 weeks of implantation. The 2 weeks following the implantation was a single-blind recovery period during which the NCP system remained off to allow for surgical recovery. The patients were told, "Stimulation may or may not be turned on immediately after surgery." Then followed a 2-week stimulation adjustment period when the NCP system was turned on, and the output current (mA setting) was gradually increased. Four weeks post implantation, i.e., after 2 weeks of treatment with VNS, the final stimulation parameters were set and were then left unchanged for the remaining 8 weeks of the first phase of the study. This phase, called the acute phase, comprised the recovery period, the stimulation adjustment period, and the fixed stimulation period and covered a total of 12 weeks. The patients were seen weekly during the recovery and stimulation adjustment periods and about once a month during the remainder of the acute phase. After completion of the acute phase, all the patients, irrespective of the outcome of their treatment, were offered continued VNS in a long-term follow-up phase of the study. Changes to the stimulation parameters were allowed during this long-term follow-up phase.

Clinical Evaluations

The baseline medical assessments included medical history; physical, psychiatric, and neurologic examinations; laboratory blood tests; lumbar puncture; ECG; and a new brain review (CT or MRI), if more than 6 months had elapsed since the last one. Psychometric tests and mood assessments were administered at baseline, during the recovery period, at the end of the acute phase (at 3 months), and at 6 months. Psychometric tests included the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog),[35] MMSE,[36] Gottfries-Brane-Steen scale (GBS),[37] Clinician Interview-Based Impression of Change (CIBIC+),[38] and the Clinical Global Impressions scale (CGI).[39] The Montgomery-Asberg Depression Rating Scale (MADRS)[40] and the Inventory of Depressive Symptomatology-Self-Report (IDS-SR)[41] were administered for assessment of affective variables. Quality of life assessments were made using the MOS 36-Item Short-Form Health Survey (SF-36)[42] at baseline, at the exit of the acute phase, and at 6 months. The physical and neurologic examinations and the lumbar puncture were repeated at the exit of the acute phase. Side effects were recorded throughout the study.

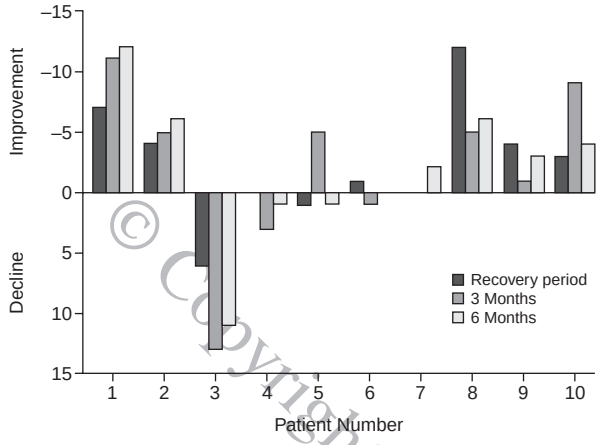
Concomitant Therapy

Treatment with ChEI was allowed if the patient had been on a stable medication regimen for at least 8 weeks before entering the study. Treatment with antidepressants and neuroleptics was also allowed for symptomatic treatment of behavioral symptoms associated with Alzheimer's disease. Short-term treatment with tranquilizers, such as short-acting benzodiazepines, was also allowed. Treatment with other cognition-enhancing drugs or experimental drugs was not allowed. The patients were not allowed to participate in concomitant clinical trials or to have participated previously in clinical trials with cognition-enhancing drugs or anti-dementia drugs. Because of the possible additive effect of VNS and cholinergic treatment on Alzheimer's disease, all patients who were not initially on ChEI therapy were offered treatment with such drugs after completion of the acute phase of the study.

Outcome Evaluations and Measurements

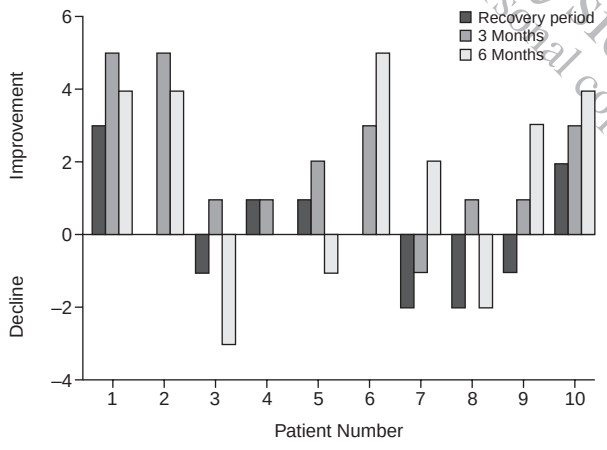
Primary efficacy parameters, *the cognitive variables,* were the median changes in ADAS-cog and MMSE scores

Figure 1. Changes in ADAS-cog Scores From the Baseline Assessment to the Assessment During the Recovery Period and After 3 Months and 6 Months of Treatment With VNS[a]



[a]Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale, VNS = vagus nerve stimulation.

Figure 2. Changes in MMSE Scores From the Baseline Assessment to the Assessment During the Recovery Period and After 3 Months and 6 Months of Treatment With VNS[a]



[a]Abbreviations: MMSE = Mini-Mental State Examination, VNS = vagus nerve stimulation.

after 3 and 6 months of treatment with VNS. The primary efficacy endpoint was the proportion of patients that responded to the treatment. A responder was defined as a patient showing improvement or no decline in MMSE or ADAS-cog score after 3 or 6 months of treatment. Responder rates based on the MMSE and ADAS-cog were evaluated separately. Secondary efficacy parameters, *the affective and behavioral variables,* were the median changes in the affective variables as measured by the MADRS and IDS-SR, the median changes in behavior as measured by the GBS, quality of life as measured by the SF-36, and the patient status as determined by the clinician's global impression (CIBIC+ and CGI). All adverse events were recorded. Because of non-normal distribution of the data, nonparametric descriptive measures were used for the analyses.

RESULTS

Cognitive Variables

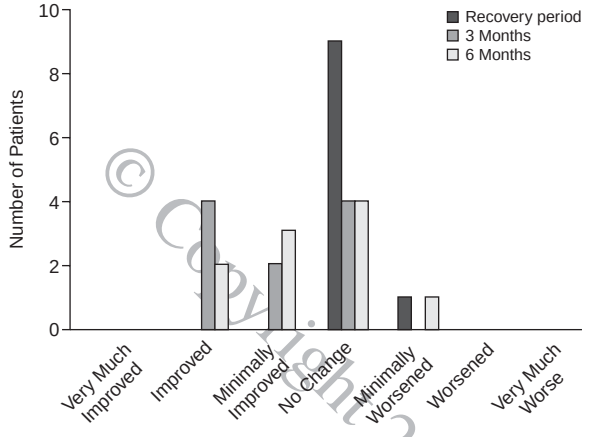
According to the ADAS-cog scores, 7 of 10 patients were responders after 3 months of treatment (Figure 1). The median improvement was 3.0 points (mean improvement = 1.9 points). After 6 months of treatment, 7 patients were responders (Figure 1), and the median improvement was 2.5 points (mean improvement = 2.0 points). In 8 of 10 patients, the cognitive functions measured by the ADAS-cog scores at 6 months showed improvement over those measured at 3 months. Testing performed during the surgical recovery period (prior to initiation of treatment) indicated an increase in score from original baseline testing in several of the patients, but 5 of the 10 patients improved further or did not decline from the recovery period at 3 months and at 6 months (Figure 1).

According to the MMSE scores, 9 of 10 patients were responders after 3 months of treatment (Figure 2). The median improvement was 1.5 points (mean improvement = 2.1 points). After 6 months of treatment, 7 patients were responders (Figure 2), and the median improvement 2.5 points (mean improvement = 1.6 points). Six patients had improvement or no decline on both the ADAS-cog and the MMSE at 3 months, and 6 patients had improvement or no decline on both assessments at 6 months (Figures 1 and 2). All 10 patients showed improvement or no decline on the MMSE from the recovery period at 3 months, and 7 showed improvement or no decline from the recovery period at 6 months (Figure 2). Four patients showed improvement or no decline from the recovery period on both the ADAS-cog and MMSE at 3 months and at 6 months (Figures 1 and 2).

Changes were also seen in global impression measures of change. According to the CIBIC+ scores, 6 patients were rated as improved or minimally improved at 3 months (Figure 3). At 6 months, 5 patients showed some level of improvement relative to baseline, 4 patients were rated as no change, and only 1 patient had worsened (Figure 3). The results of the CGI were in agreement with those of the CIBIC+.

Four of 10 patients were taking ChEI at the start of the study (Table 2). They had been stable on these medications for at least 12 months. Three of the 4 were responders on the ADAS-cog at 3 months, with all 3 showing an improvement in score. At 6 months, 3 of the 4 were responders on the ADAS-cog, with 2 showing an improvement in score. Three of the 6 patients who did not take ChEI during the acute phase of the study began to take these medications during the follow-up phase in an urge to improve further

Figure 3. Distribution of Patients Showing Improvement, No Change, or Worsening of the Global Impression Relative to Baseline as Scored by the CIBIC+ During the Recovery Period and After 3 Months and 6 Months of Treatment With VNS[a]



[a]Abbreviations: CIBIC+ = Clinician Interview-Based Impression of Change, VNS = vagus nerve stimulation.

(Table 2). Only 1 of these 3 patients began taking medication prior to the 6-month visit assessments, with 2 beginning cholinergic treatment after 6 months of treatment.

All 10 patients chose to continue the treatment at the end of the acute phase. They were evaluated 6 months after implantation and will be followed further.

Behavioral and Quality of Life Variables

Baseline behavior and mood were not significantly impaired in this patient group. The median MADRS score was 3 (range, 0–8; maximum score = 60) at baseline, 2 (range, 0–8) at 3 months, and 2.5 (range, 0–6) at 6 months. The differences in median scores between the baseline and the 2 endpoint ratings were not significant, although a trend toward improvement was noted. There were no significant changes in IDS-SR scores between the ratings at 3 and 6 months and the baseline ratings.

The median GBS score was 19 (range, 7–32; maximum score = 162) at baseline, 14.5 (range, 6–31) at 3 months, and 12.5 (range, 5–41) at 6 months. The differences between the baseline and the 2 endpoint ratings were not significant, nor were there any significant differences in GBS subscores (cognitive, emotional, motor, and behavioral symptom variables) between the ratings at 3 and 6 months and the baseline ratings.

No changes in quality of life variables (SF-36) were found when the ratings at 3 and 6 months were compared with the baseline ratings.

Stimulation Parameters

All 10 patients reached an output current of 0.75 mA during the stimulation adjustment period. One patient, however, experienced intolerable pain and irritation in the throat with stimulation during the acute study. The output current was lowered to 0.5 mA, and the pulse width was changed from 500 to 250 μsec. This alleviated the symptoms, and the patient was able to continue the stimulation treatment. Stimulation parameters were otherwise maintained through the acute phase of the study and at 6 months of treatment.

Table 2. Use of Cholinergic Treatments in 10 Patients With Alzheimer's Disease

Patient	Cholinergic Use at Baseline	Change in Cholinergic Use During Study (through 6 mo)	Change in Cholinergic Use at 6 Mo
1	No	No	No
2	No	Added at 3 mo	No
3	No	No	Added at 6-mo visit
4	No	No	No
5	Yes	No	Dose increased at 6-mo visit
6	Yes	No	No
7	No	No	Added at 6-mo visit
8	Yes	No	No
9	No	No	No
10	Yes	No	No

Safety Profile

In general, the treatment with VNS was well tolerated. All the patients chose to continue with the treatment after 6 months. The most common side effect was hoarseness. This side effect occurred only during stimulation, i.e., for 30 seconds at 5-minute intervals. After 3 months of treatment, the patients no longer reported this symptom as a problem but had adapted to it. Other adverse events that were reported in more than 1 patient and that were considered possibly, probably, or definitely related to stimulation or implantation were hematoma in the left chest/mammae area, swelling over the generator area, diffuse itch in the skin of the chest, and dizziness. One patient reported pain and irritation in the throat with stimulation, which was relieved by deactivating the stimulator for a few hours and then resuming stimulation at a lower output current and pulse width as described above.

Two other side effects were probably also related to the implantation: One patient had signs of lead site inflammation, which resolved spontaneously, and 1 patient fainted 2 days post surgery. The latter was examined by a surgeon and a neurologist within a few hours of the fainting episode, but no cause could be identified. She recovered spontaneously.

On the other hand, 2 side effects were judged to be unrelated to the implantation or the VNS. One patient experienced increasing anxiety when her husband went to his job. This adverse event was resolved by hospitalization. No other action was required. One patient, who had a history of 2 falls within 1 year, fell in her home. She was

examined by an internist in the emergency unit and was discharged after 1 day of hospitalization. The diagnosis was commotio cerebri, although no clear neurologic signs were found.

DISCUSSION

This pilot study is the first to document a possible effect of VNS on cognitive functions in patients with mild or moderate Alzheimer's disease. At both 3 and 6 months, the treatment with VNS resulted in an improvement in cognitive functions, as measured by the median (and mean) change in the total ADAS-cog score. In addition, the measurements at 6 months showed an improvement in cognitive functions over the measurements at 3 months. The ADAS-cog includes testing of several cognitive domains and is the instrument of choice in most clinical trials that include Alzheimer's disease patients. A positive effect on cognition was also found using the MMSE. This instrument is often included in clinical trials as a measure of cognitive functioning, but is much briefer and therefore less sensitive to change than, for instance, the ADAS-cog. The MMSE score was used as an inclusion criterion, and therefore, the results should be used cautiously. Response based on the MMSE, which was administered by a different clinician from the one who administered the ADAS-cog, was comparable to response based on the ADAS-cog. The changes in cognitive functions were supported by the clinical global impression. Both the CIBIC+ and the CGI ratings showed that several of the patients had improved with VNS.

A limitation of the study was that no control group was included, and, thus, random or placebo effects cannot be excluded. However, data from several previous placebo-controlled studies on Alzheimer's disease are available for comparison. A 1-year placebo-controlled trial with sabeluzole revealed a decline of 2 to 3 points per 6 months in the ADAS-cog scores of the placebo-treated group.[43] Most placebo-controlled clinical trials with ChEIs reveal a decline in the ADAS-cog score of about 2 to 3 points over 6 months in the placebo-treated group.[44–47] In comparison with this result, treatment with VNS seems promising. Use of an active control group (high vs. low stimulation), a delayed treatment group, or a standard of care comparison group may be necessary to rule out the possibility of a placebo effect of VNS. It is important to note, though, that long-term treatment outcomes with VNS are important in Alzheimer's disease, and use of a long-term delayed treatment group or low stimulation group is ethically questionable.

Early improvements in Alzheimer's disease clinical studies due to placebo effects are not uncommon. In this study, cognitive testing during the recovery period (prior to initiation of VNS) allowed the observation of improvements following surgery but prior to initiation of VNS treatment. These improvements might reflect a "placebo effect" of the surgery or treatment, as patients were not told whether they were receiving stimulation during this period. Alternatively, stimulation of the vagus during the surgical procedure might potentially have a therapeutic effect. While this possibility may seem unlikely, it has been observed in patients with epilepsy and cannot be ruled out. Random variations in performance and practice effects from baseline testing should also be considered in this small sample of patients.

While improvements during the recovery period were observed in several patients, it may be questioned to what extent placebo effects can be present at 6 months in a neurodegenerative disorder that entails a continuous cognitive decline. The response to placebo in the clinical trials with ChEIs reveals an effect duration of only 1 to 2 months,[44–47] and, thus, it does not seem probable that the placebo effect would last as long as 6 months. Any effect at 6 months would therefore most likely be due to the active treatment. In this study, 5 and 7 patients had further improvement or no decline from the recovery period at 6 months on the ADAS-cog and MMSE, respectively, and 4 had further improvement or no decline on both assessments at 6 months.

Possible explanations for an improvement in cognitive function in Alzheimer's disease with VNS are based on the known anatomical projections of the vagus nerve to the locus ceruleus (LC). Afferent fibers of the vagus terminate on the nucleus tractus solitarius (NTS), which provides ascending projections to the forebrain largely through the parabrachial nucleus (PBN) and the LC.[33] Animal studies demonstrate that VNS activates the LC, the major nucleus of origin for noradrenergic projections in the brain. This is evidenced both by c-*fos* expression following VNS[48] and increased neuronal firing within the LC.[49] Lesion of the LC counters the anti-seizure properties of VNS, demonstrating that the LC is a critical part of the neural pathway for the therapeutic effects of VNS in epilepsy.[50]

In addition to atrophy of the basal forebrain cholinergic system, marked neuronal loss occurs within the LC in Alzheimer's disease.[51] Reduction of norepinephrine (NE) concentration in the temporal cortex is significant in Alzheimer's disease and correlates with the degree of cognitive impairment.[52] Recent data suggest that cholinergic atrophy alone may not be sufficient to cause marked changes in cognition and cortical activity typical of Alzheimer's disease, but that concurrent monoaminergic and cholinergic deficits promote such disturbances.[53] This theory predicts that monoaminergic stimulation or combined cholinergic-monoaminergic enhancement may be more effective at reversing the cognitive disturbances associated with Alzheimer's disease than cholinergic treatment alone.

In addition to its role as a classical neurotransmitter, NE inhibits inflammatory activation of microglial cells

and is postulated to be an endogenous anti-inflammatory agent.[54] Loss of LC neurons and depletion of NE augment inflammatory responses to amyloid beta, suggesting that reduced NE in Alzheimer's disease may contribute to increased inflammation and neuronal cell death.[55] It has been suggested that LC dysfunction occurs early in Alzheimer's disease and precedes gradual loss of LC projections. Stimulation of the LC with VNS, particularly in less severe stages of disease progression, could potentially increase cortical concentration of NE, dampen neuroinflammatory events associated with Alzheimer's disease, and possibly also slow disease progression. Analysis of CSF before and after VNS treatment is necessary to investigate this hypothesis.

It might be argued that improvement in cognitive function observed in this study could be attributed to a nonspecific alerting effect of the stimulation due to perception of the stimulation by the patient or to improvements in mood. Stimulation parameters used in this study were lower than those used in studies of epilepsy, and the patients did not report sensation of stimulation at 3 and 6 months of treatment. It is therefore unlikely that the cognitive effects in this study are attributable to a nonspecific alerting effect. Cognitive effects due to improvements in mood are also unlikely in this patient group in that baseline mood disturbances were not prevalent.

In this study, both patients currently taking ChEIs and patients not currently taking ChEIs were treated with VNS. The 4 patients that were on ChEI therapy during the acute phase of the study had been stable on that medication and dose for more than 12 months prior to entering the study. Therefore, any improvements in these patients from study baseline would be attributable to the addition of VNS rather than the cholinergic treatment, even if the cholinergic treatments were still providing benefit. At 3 months, all 4 patients taking concomitant ChEI responded to the additional VNS treatment on either the ADAS-cog or MMSE, and at 6 months, 3 of them were still responders on the ADAS-cog. Of the 6 patients not taking ChEIs at the start of the study, 3 showed improvement on the ADAS-cog at 3 months, 2 declined, and 1 had no change from baseline. One patient added cholinergic treatment at 3 months in an attempt to improve further. This patient had shown a 5-point improvement on both the MMSE and ADAS-cog at 3 months, with a further 1-point improvement on the ADAS-cog and 1-point decline on the MMSE from 3 months to 6 months. These results suggest a positive effect of VNS treatment on cognitive functioning in patients with Alzheimer's disease with or without cholinergic treatment. Additional studies are needed to determine if combined treatment with VNS and ChEIs is more effective than VNS or ChEI treatment alone. VNS treatment may prove beneficial as an alternative for Alzheimer's disease patients who do not tolerate ChEIs or as an adjunctive treatment to ChEI medication to further boost cognitive function. VNS treatment does also have a clear advantage for patients with memory disturbances: they do not have to remember to take their medicine.

In addition to enhancing cognition function, management of Alzheimer's disease patients often requires treatment of behavioral and psychiatric symptoms of dementia (BPSD) including depression. VNS treatment has been shown to have antidepressant properties.[19,56,57] In the European countries, VNS treatment is today an approved treatment alternative in treatment-resistant and bipolar affective disorders. VNS may therefore prove beneficial for treatment of both cognitive and behavioral symptoms in patients with Alzheimer's disease. In the present study, 2 instruments were used to investigate the effects of VNS treatment on affective symptoms in patients with Alzheimer's disease: the MADRS, an evaluator-completed assessment of the overall severity of depression, and the IDS-SR, a patient-completed questionnaire concerning the symptoms of mood and depression. Baseline mood and behavioral disturbances were not significant in this patient group, so no acute improvement of these symptoms could be evaluated. Only 1 patient in this study had previously suffered from episodes of major depression. She was being treated with antidepressants when she entered the study. However, no significant changes in affective symptoms were found for the group as a whole, as measured by the median changes in MADRS and IDS-SR scores, nor were there any significant changes in scores on the GBS instrument, which was included to identify changes in behavioral symptoms. These results are encouraging in that no decline in mood or behavior was observed. Such decline is otherwise both common and burdensome in Alzheimer's disease patients.

The SF-36 was included to identify changes in quality of life. Previous studies of patients with epilepsy and depression have shown an increase in quality of life with VNS treatment.[56] In the present study, no significant changes in quality of life measures were found. Several patients and spouses anecdotally reported increases in cognitive measures that secondarily led to an improvement in quality of life. However, the statistical analysis could not verify this impression. Decline in quality of life is a tragic feature of Alzheimer's disease, and the apparent stabilization of quality of life in this small group of patients is clinically meaningful. Future studies including larger groups of patients with Alzheimer's disease should investigate this aspect further.

In general, the VNS treatment was well tolerated. All recorded side effects resolved themselves spontaneously or with minor actions, such as adjustment of the stimulus parameters. No patient required an explantation or disconnection of the pulse generator. In 1 case, the stimulation was turned off because of pain, but only for a few hours. Two patients were hospitalized, 1 for social reasons and 1 because of a fall, and neither hospitalization

was determined to be related to VNS. None of the patients met with a life-threatening adverse event, and all the patients completed the acute phase and have continued VNS treatment thus far in the follow-up phase of the study. According to the results of this study, there seem to be no adverse events associated with VNS specific to treatment of patients with Alzheimer's disease. The choice of all the patients to continue the treatment after 3 and 6 months further suggests that VNS is a well-tolerated and safe treatment for patients with Alzheimer's disease.

To conclude, the results of this open-label pilot study suggest a positive effect on cognition of VNS treatment in patients with Alzheimer's disease. As the decline in cognitive functions was less than could be expected for Alzheimer's disease patients in a 6-month period, VNS treatment seems promising for treating Alzheimer's disease. Even in patients who had been on a stable ChEI regimen for more than 12 months, the VNS treatment resulted in an improvement in cognitive functions. This suggests that VNS treatment may be used as additional therapy in Alzheimer's disease patients treated with ChEI. No clear changes, whether decline or worsening, were found in affective, behavioral, or quality-of-life measures. However, several spouses reported improvements in these aspects, which suggests that further assessment of VNS effects on mood in Alzheimer's disease is warranted. The treatment was safe and well tolerated, and all the patients chose to continue with VNS treatment after the scheduled 6 months. In the light of the positive results of this pilot study, a study of VNS treatment in a larger sample of Alzheimer's disease patients is clearly warranted.

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