Overview of the Clinical Applications of Vagus Nerve Stimulation

J. P. Beekwilder†‡ and T. Beems*‡*

Abstract: Vagus nerve stimulation (VNS) has become an established therapy for difficult-to-treat epilepsy during the past 20 years. The vagus nerve provides a unique entrance to the brain. Electrical stimulation of this structure in the cervical region allows direct modulative access to subcortical brain areas, requiring only minimally invasive surgery with low risks involved. VNS therapy has shown to reduce epileptic seizures both in number and severity in a group of patients not responding to antiepileptic drugs. The effects are accompanied by an atypical set of central side effects. After the success of the VNS therapy with epilepsy, the technique has been applied to a wide variety of disorders, ranging from major depressive disorder to Alzheimer's disease. The results of several of these are promising. In this review, the results as well as the rationale for the different applications of VNS are discussed.

Key Words: Vagus nerve, Neuromodulation, Psychiatric disorders, Neurologic disorders, Brain stimulation.

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In vagus nerve stimulation (VNS) therapy, a bipolar helical electrode is placed around the cervical vagal nerve (tenth cranial nerve) at the level of about the fifth to sixth cervical vertebra, which is stimulated in a regular cycle. These pulses are generated by a connected pulse generator placed in the chest wall (Fig. 1).

The surgical technique has been extendedly described (Reid, 1990). In summary, the vagal nerve is explored over a length of approximately 3 cm in the left carotid sheath between the carotid artery medially and the internal jugular vein laterally, just above the crossing of the omohyoid muscle (i.e., at the level of the sixth cervical vertebra). A spiral electrode consisting of an anchor, an anode, and a cathode is placed around the nerve (in this sequence in caudal-cranial direction) and the connected cable is (with some loops to reduce traction) tunneled subcutaneously to and connected with a pulse generator that is placed in a subcutaneous or submuscular pocket in the left chest wall.

The use of VNS in humans started in the late 1980s and many publications of its use showed up in the last 20 years.

History of VNS in Humans

VNS therapy was introduced in humans in 1988 for the treatment of therapy-resistant epilepsy by Penry and Dean (1990). Epilepsy is a common neurologic disorder, characterized by abnormal electrical discharges in the brain, resulting in seizures, possibly with involuntary movements of different extremities and/or loss of consciousness and/or cognitive symptoms. The outcome of the first treated patients with medically intractable complex partial seizures was reported at the annual meeting of the American Epilepsy Society in 1989. Those preliminary results indicated a reduction in seizure frequency and a decrease in the duration and severity of seizures, without serious complications or mechanical failures (Wilder, 1990).

In the subsequent years, several clinical trials were set up to assess the efficacy, safety, and tolerance of VNS therapy. In 1995, the VNS study group published a randomized controlled study in 114 patients, with predominantly intractable partial seizures, comparing two VNS paradigms (Vagus Nerve Stimulation Study Group, 1995). The paradigms were high (therapeutic) stimulus intensity versus low (nontherapeutic) intensity. The high-intensity group received 0.25 to 3 mA pulses at 20 to 50 Hz, with 500-μs pulse width, 30 to 90 seconds "on" time and 5 to 10 minutes "off" time, compared with the low-intensity group, which received 0.25 to 2.75 mA pulses at 1 to 2 Hz, with 130-μs pulse width, 30 seconds on time, and 60 to 180 minutes off time. The latter was chosen to provide a stimulus sensation to the patient to allow better blinding of the study. Patients in both groups were followed up for 14 weeks. During the last 12 weeks of treatment, the "high" group had a significantly greater reduction in seizure frequency compared with their baseline as well as to the "low" group. Thirty-one percent of patients receiving the high stimulation had a reduction of 50% or more in seizure frequency. All patients elected to continue treatment in the extension phase of the study.

In 1998, a similar setup was used involving 198 patients, with complex partial seizures, receiving either high or low stimulation for a period of 12 to 16 weeks (Handforth et al, 1998). Compared with low stimulation, high stimulation significantly reduced overall seizure frequency. The authors also report a reduced amount of partial-onset seizures involving alteration of awareness (complex partial with secondarily generalized convulsions). Furthermore, global assessments of well-being showed greater improvements in the high group.

As a result of these clinical studies, VNS therapy was approved as a treatment for medically refractory epilepsy in Europe in 1994 and in the United States and Canada in 1997. The evidence supporting VNS for epilepsy as safe and effective was classified as class I in 1999 by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (Fisher and Handforth, 1999).

Twenty-four patients with generalized epilepsy were included in a study by Labar et al. (1999). A mean reduction of 46% in seizure rate was reported in the 3 months after VNS implantation compared with 1 month baseline before onset. Twenty-two patients improved with 11 patients having >50% seizure reduction.

Long-term results were studied by Morris and Mueller (1999). Patients who participated in previous clinical studies were enrolled in this open-label, long-term efficacy/tolerability study. The study that included 440 patients showed an increased efficacy over time, with more patients reaching a 50% seizure reduction after 2 and 3 years, whereas adverse events became less common during the

From the *Twin – Institute for Neuromodulation, Groesbeek, The Netherlands; †Biomedical Signals and Systems, University of Twente, Enschede, The Netherlands; and ‡Department of Neurosurgery, University Medical Centre St Radboud, Nijmegen, The Netherlands.

Address correspondence and reprint requests to J. P. Beekwilder, Twin – Institute for Neuromodulation, ULC Dekkerswald, P.O. Box 66, 6560 AB Groesbeek, The Netherlands; e-mail: beekwilder@neuromodulation.nl.

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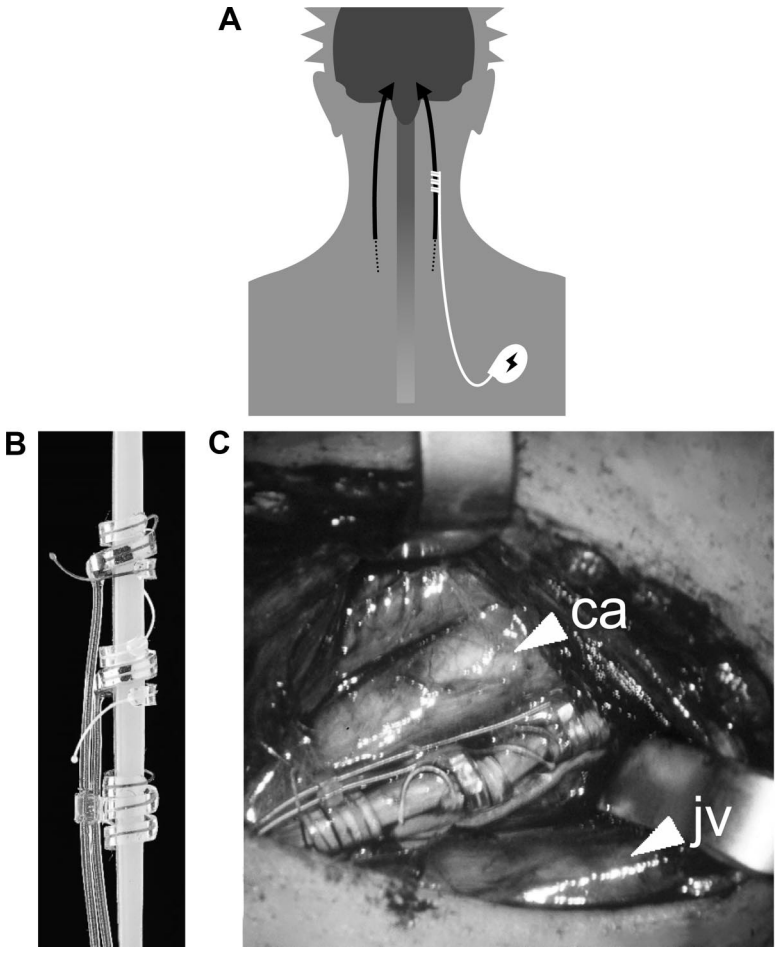

FIGURE 1. The VNS system. (**A**) Schematic drawing of the VNS pulse generator and electrode lead in the human body. Placement of the system is standard on the left side of the body. (**B**) The three helical parts of the electrode in detail. (**C**) Intraoperative picture of electrode placed around the vagus nerve. Arrowheads indicate medially the carotid artery (ca) and laterally the internal jugular vain (jv). Location of the patient's head is on the right side of the picture.

3-year period of follow-up. The further decrease in seizure activity from year 1 to 2 could not be explained by adjustments in parameter settings. Furthermore, a low withdrawal rate was noted, even after battery depletion. This means that patients were willing to undergo renewed surgery to continue therapy. This is a clear indicator for the patient satisfaction concerning the therapy. Long-term data up to 12 years of VNS experience showed that the therapeutic effects of VNS lasted for longer periods (Uthman et al., 2004).

In addition to a reduction in seizure frequency, Tatum et al. (2001) found that seizure duration and postictal recovery improved as a result of VNS in 15 of 21 patients. Similar results were observed by McHugh et al. (2007), with 19 of 48 patients reporting improvement in ictal and/or postictal severity. Hence, therapeutic effects of VNS are underestimated if only seizure frequency is taken as an outcome measure. In addition, Tatum found a reduction in the number and dosage of antiepileptic drugs.

Besides the programmed stimulation at set intervals, patients have the possibility to initiate extra stimulation using a magnet that comes with the VNS system, typically when a seizure is anticipated or is in progress. Morris et al. (2003) looked at the magnet use of VNS users. Roughly half of the patients received benefit from the on-demand stimulation. This seizure improvement was unrelated with seizure frequency. It was postulated that besides direct therapeutic effects of the additional stimulation provided by the magnet, patients gain a greater sense of control over their seizures. This could represent a reversal of "learned helplessness," which may occur in patients with pharmacoresistant epilepsy of long duration (Hermann et al., 1996). The magnet-induced stimulation is typically 0.25 mA higher than the normal intermittent vagus stimulation. However, Tatum and Helmers (2009) suggested that the magnet stimulation should be titrated independently.

VNS in Pediatrics

At first, VNS therapy was meant for adults. However, many studies have been performed with adolescents and young children.

In 1997, the effects up to 30 months of VNS therapy in 19 children (mean age, 10.2 years) with refractory epilepsy were described (Hornig et al., 1997). Ten patients had a reduction in seizures of >50% and six patients had >90%. In another study, Parker et al. (1999) said that VNS did not significantly improve seizure frequency, severity, adaptive behavior or the EEG findings in a 12-month study with 16 children. However, the review of the 2-year results in the addendum of the study showed much better results, which also indicates that the efficacy of VNS therapy improves in the second year of treatment, instead of wearing off, as is the case in most therapies for difficult-to-treat epilepsies.

One hundred twenty-five children younger than 18 years implanted with the VNS system were evaluated in a retrospective study (Helmers et al., 2001). On average, the children were 11.8 years old, with 41 children younger than 12 years. The overall seizure reduction after 3 and 6 months was 36% and 45%, respectively. Besides the common adverse events reported in adults, unique side effects in this age group were drooling and increased hyperactivity. A retrospective study with 69 children, aged at im-

plantation on average 10.7 years old, showed that 55% had a worthwhile improvement after an average follow-up of 3.8 years (Kabir et al., 2009).

The results of children younger than and older than 12 years were compared retrospectively by Murphy et al. (2003). No differences were found in the seizure control in these two age groups. More than 50% seizure reduction was achieved in 23 of the 50 and 16 of the 34 for the younger and older groups, respectively.

The impact of VNS therapy on cognition, quality of life, behavior, and mood was studied in 15 children with therapy-resistant epilepsy (Hallbook et al., 2005). All patients, except one, were mentally retarded. Besides seizure control, the results showed improvement (in parents' conception) in quality of life, behavior, and mood after onset of VNS. The improvements were not related to the antiseizure effects. No changes in cognition were found.

Majoie et al. (2005) looked at the follow-up of a group of 19 patients with Lennox-Gastaut syndrome or Lennox-like epilepsy. After 24 months, a mean seizure reduction of 20.6% was found and four of the 19 patients had a seizure reduction of >50%. The largest reduction was found in patients with the highest baseline mental function.

In the group of young children, Zamponi et al. (2008) described six children (<3 years) with catastrophic epilepsy and status epilepticus. One patient had no significant seizure reduction after 17 months. The other five patients all had >40% reduction in seizures of which two had >75% reduction. Six patients with refractory multifocal epilepsy younger than 5 years were described by Blount et al. (2006). One patient had no change in seizure status, five improved with two being seizure free.

Side Effects and Adverse Events of VNS

With more patients undergoing VNS therapy, more became known about the adverse events associated with the therapy. The side effects were first described by Ramsey et al. (1994). Ramsay et al. reported no serious adverse events in 114 patients. Common side effects associated with VNS were primarily limited to the periods in which the stimulator was actually delivering pulses. These were hoarseness, throat pain, and coughing. In addition to these statistically significant side effects, several events seemed to be VNS related. These included abdominal pain, nausea, shortness of breath, and chest pain.

The side effects collected from patients enrolled in five previous clinical trials were published by Morris and Mueller (1999). The most common adverse events after 1 year were hoarseness (28%) and paresthesias in throat-chin region (12%), after 2 years hoarseness (19%) and cough (5.9%), and after 3 years shortness of breathe (3.2%). In general, the side effects are well tolerated.

Ben-Menachem (2001) concluded that VNS side effects are usually related to stimulation itself and often improve with time. Unwanted side effects are easy to control by reducing the stimulation intensity. It does not cause central nervous system side effects, such as tiredness, psychomotor slowing, irritation, and nervousness, common in antiepileptic drugs.

Depression and VNS

Depression is a mental disorder characterized by sadness, loss of interest in normal daily activities, feelings of dejection and hopelessness, and diminished ability to experience pleasure. Estimates are that worldwide 15% to 17% (World Health Organization International Consortium in Psychiatric Epidemiology, 2000) of the population will have a period of depression during their lifetime. The majority of the major depressive episodes can be treated pharmacologically satisfactorily. Roughly, 30% of the people with major depressive episodes are not responding to medication. Part of this group can be satisfactorily treated, although often temporary, with electroconvulsion therapy.

Mood changes apparently unrelated to seizure improvement were a clue that VNS may also have antidepressant effects. Furthermore, a number of anticonvulsant drugs, such as carbamazepine and valproate, have been successfully used as antidepressants. Finally, VNS resulted in altered neurotransmitter and metabolite concentrations. Concentrations of γ-aminobutyric acid, glutamate, serotonin, and norepinephrine, which are involved in mood, showed to be affected by VNS (Ben-Menachem et al., 1995).

Therefore, an open study by Harden et al. (2000) was performed on the effect of VNS on mood of patients with epilepsy. With several depression rating scales, patients were tested before and after 3 months of VNS. The patients started with scores associated with mild depression. After 3 months, a significant reduction in the scores was found. In the comparison group, consisting of patients on a stable antiepileptic drug regimen, no change in scores was found. No differences were found between responders and nonresponders with respect to the seizure reduction, indicating that the antidepressant effect could not be attributed to the antiepileptic effects of VNS.

Elger et al. (2000) conducted a study with 11 patients in a randomized control trial. Five patients received low-intensity stimulation and six patients received high intensity. On a stable antiepileptic drug regimen, a significant reduction in depressive symptoms was found after 3 and 6 months, which seemed independent of seizure attenuation because of VNS.

The first report of VNS with patients with nonpsychotic major depressive or bipolar disorder came in a open-label, nonrandomized study (Rush et al., 2000). Ten weeks after onset of VNS therapy, 12 of 30 patients had a ≥50% reduction in the Hamilton-28 Depression Rating Scale, with five patients in complete remission. The extended version of that study was published a year later with 59 patients (Sackeim et al., 2001b). The results showed that VNS had a slightly less persisting antidepressant effect compared with the initial findings. The authors contributed this discrepancy to the higher degree of treatment resistance in the second group of patients. They found that patients with a higher number of failed adequate trials had a decreased chance of responding to VNS therapy. Therefore, they suggested that VNS would be most appropriate in patients with low-to-moderate levels of treatment resistance.

A large randomized controlled pivotal study was performed by Rush et al. (2005a). They compared 10 weeks of VNS stimulation versus 10 weeks of sham stimulation in a group of 222 patients with nonpsychotic major depressive disorder or patients in the depressed phase of bipolar disorder. Ten weeks after the onset of VNS, no statistical difference was found between the groups of patients, which had been assigned to the active stimulation group or to the sham group, with 15.2% and 10.0% response rates, respectively. The authors suggested that 10 weeks of VNS may not have been enough to achieve clinically meaningful benefit. The patients from the acute study were also evaluated during a 12-month follow-up (Rush et al, 2005b). The response and remission rates increased steadily over the 12-month period to ~30% and ~15%, respectively (as was seen in the epilepsy patients' population). However, a control group was missing for these long-term results. A comparison for this group was made by George at al. (2005) who looked at the 12 months results from a group of patients who received treatment as usual without VNS therapy. At onset the two groups had similar demographics and disease history, but after 12 months the treatment as usual group's response rate was significantly smaller with just 13% of the patients having a depression score reduction of 50% or more. The 2-year outcomes for bipolar versus unipolar treatment-resistant depression of the participants

enrolled in the randomized control trial indicated that both short and long-term effects were similar for the two groups (Nierenberg et al, 2008). The study also showed no differences between the 12 and 24 months data.

The durability of the effects was studied to find whether the clinical benefits would persist (Sackeim et al., 2007). The depression scores were determined up to 24 months showing a lasting effect of the VNS therapy. This effect was the same for both early responders (≥50% reduction of depression score after 3 months of VNS therapy) and late responders (≥50% reduction of depression score after 12 months of VNS therapy).

Recently, the results of an European uncontrolled multicenter study were published (Schlaepfer et al., 2008). Seventy-four patients with treatment-resistant depression received VNS therapy and were followed up for 12 months. After 3 months of VNS therapy, 37% of the patients had responded, which gradually increased to 53% after 12 months with a remission rate of 33%. The study design had been similar to the first reports of Rush et al. (2000) and Sackeim et al. (2001b). The results found by Schlaepfer et al. showed higher response rates. The authors contributed this difference to lower measures of baseline depressivity in the latter study.

A list of the major clinical studies of VNS in epilepsy and depression is given in Table 1.

TABLE 1. Major Studies of VNS as a Treatment for Epilepsy and Depression

Description	References
VNS and epilepsy	
Randomized controlled trial in 114 patients with intractable partial seizures	Vagus Nerve Stimulation Study Group (1995)
Randomized controlled trial with 198 patients with complex partial seizures	Handforth et al. (1998)
Prospective open-label trial of VNS in 24 patients with generalized epilepsy	Labar et al. (1999)
Long-term results in open-label study of 440 patients	Morris and Mueller (1999)
Ultra long-term results in retrospective study in 48 patients intractable partial epilepsy	Uthman et al. (2004)
Prospective study about VNS and drug reduction in 21 patients	Tatum et al. (2001)
Ictal and postictal improvements by VNS in retrospective study with 48 patients	McHugh et al. (2007)
VNS in pediatrics	
Retrospective study of 19 children who received VNS treatment for intractable epilepsy	Hornig et al. (1997)
Prospective study of VNS effects in 16 children with epileptic encephalopathies	Parker et al. (1999)
Retrospective study of effectiveness, safety, and tolerability of VNS in 125 children	Helmers et al. (2001)
Retrospective study of 100 children with VNS	Murphy et al. (2003)
Nonseizure frequency-related effects of VNS in 15 children with epilepsy	Hallbook et al. (2005)
Longitudinal observational prospective study in 19 children with Lennox-Gastaut syndrome	Majoie et al. (2005)
Case reports about VNS in 6 young children (<3 yr)	Zamponi et al. (2008)
Case reports about 6 children younger than 5 yr with VNS	Blount et al. (2006)
VNS and depression	
Open study on the effect of VNS on mood in 20 epilepsy patients	Harden et al. (2000)
Randomized controlled trial with 11 epilepsy patients with depressed mood	Elger et al. (2000)
Open-label study with 30 patients with nonpsychotic major depression	Rush et al. (2000)
Extension of the Rush (2000) study with 59 patients	Sackeim et al. (2001a)
Randomized controlled trial with 222 patients with major depressive disorder	Rush et al. (2005a)
12-mo follow-up of the Rush (2005a) study	Rush et al. (2005b)
Comparison of 12-mo outcome form Rush (2005b) with TAU group	George et al. (2005)
Follow-up of 24 mo for Sakeim (2001a) and Rush (2005a) studies	Sackeim et al. (2007)
Multicenter study with 74 patients with treatment resistant depression	Schlaepfer et al. (2008)

VNS and Migraine

Migraine is a neurologic syndrome accompanied with recurrent episodes of painful, usually unilateral headaches and nausea. Anticonvulsants and antidepressants such as gabapentin and topiramate are among the drugs that are effective in prophylaxis of migraine. During the years, several cases were described in which the migraine in patients receiving VNS therapy for either epilepsy or mood disorder seemed to be positively affected, indicating effectiveness in this disorder.

One case is described by Sadler et al. (2002) about a 42-year old with seizures, dating back to childhood. Since his late teens, he suffered migraine attacks. After onset of VNS therapy, the migraine attacks reduced in frequency from 2.7 a month pre-VNS to a total of three attacks in 13 months post-VNS. The striking reduction in migraine episodes was only accompanied by a modest improvement in seizure control.

Four cases were described in which patients who received VNS therapy for intractable seizures had concomitant common migraine (Hord et al., 2003). One patient with two to three migraine episodes per month pre-VNS reported no further migraine attacks after implantation. Patient 2 went from two to three migraine episodes per week to 1 to 2, with a slight relief in average severity. The third patient had two to three migraine episodes per month pre-VNS and went to one episode every 2 to 3 months post-VNS. The average pain rating for the episodes went down substantially. Finally, patient 4 started out with one to two episodes per week. After VNS, this was around once a month with the pain much relieved compared with before implantation.

Mauskop et al. (2005) described four patients with migraine who had the VNS system implanted. Two patients reacted excellent with a reduction in the number of episodes as well as in the severity. One patient was not able to tolerate VNS and a fourth patient reacted well in the first 3 months but fell back to baseline afterward.

In 2008, a report was published in which the episodes of 10 patients with migraine were recorded before and after onset of VNS therapy (Lenaerts et al, 2008). The VNS systems were implanted for concomitant intractable epilepsy or mood disorders. Eight of the 10 patients had at least 50% reduction in the frequency of migraine attacks, and five of them became migraine free. The authors compared the effects of VNS on migraine with the improvement on

either seizure control or depression rating. Neither of these seemed to correlate.

Recently, Cecchini et al. (2009) reported about four patients with daily chronic migraine associated with depression. Two patients showed marked improvements after 6 and 14 months follow-up, going to just two or three attacks a month. A third patient showed improvements initially, but fell back after 4 months. One patient did not see a reduction in headaches, despite an improvement in mood.

Alzheimer's Disease and VNS

Alzheimer's disease is the most common form of dementia and a progressive disorder characterized by deterioration of cognitive functions. VNS had been shown to have a positive effect on cognition in the form of motor speed, psychomotor function, language, and executive functions after 10 weeks of stimulation (Sackeim et al., 2001a). Furthermore, VNS affects the level of different neurotransmitters, known to be changed in Alzheimer's disease (Wenk, 2003), and activates brain regions that are usually degenerated in these patients. Therefore, a study was started with 10 patients diagnosed with probable Alzheimer's disease (Sjogren et al., 2002). Response was defined as improvement or absence of impairment in Alzheimer's Disease Assessment Scale-cognitive subscale and Mini-Mental State Examination scores after 3 and 6 months. Three months after onset of VNS therapy, seven of the 10 and nine of the 10 patients responded according to the Alzheimer's Disease Assessment Scale-cognitive subscale and Mini-Mental State Examination scores, respectively. After 6 months, seven of the 10 patients were responding for both assessment methods. Overall, VNS was well tolerated and seemed to have a positive effect on the cognition of Alzheimer's disease patients.

A follow-up and expansion of the Sjogren study was published by the same group (Merrill et al., 2006). In this report, 17 patients were followed up. After 12 months, seven patients improved and 12 patients did not worsen, as determined with the Alzheimer's Disease Assessment Scale-cognitive subscale and Mini-Mental State Examination scores. Behavior and mood disturbances, usually associated with disease progress, were not seen. Instead, modest improvement in mood and quality-of-life variables were found. After 12 months of VNS treatment, a slight reduction in cerebrospinal fluid (CSF) tau was observed (4.8%), indicating an alleviation of the synaptic degeneration. No changes were observed in Aβ42. However, the concentration of phospho-tau, a more specific biomarker for Alzheimer's disease (Blennow and Hampel, 2003), in the CSF increased by 5%.

Although preliminary, these results warrant further investigation about the application of VNS therapy in Alzheimer patients.

Multiple Sclerosis and VNS

The first report about VNS therapy in multiple sclerosis (MS) was published in 2005. A single patient with persistent cerebellar tremor as a result of MS was implanted with the VNS system (Marrosu et al., 2005). The tremor improved with low-cycle stimulation settings. The authors suggested that lower-intensity VNS cycling and modified time-equivalent on-off periodic stimulation could disrupt the altered rhythmicity of inferior olive firing, a crucial factor in cerebellar tremor.

In 2007, a study was published by the same group about three patients with MS with postural cerebellar tremor and dysphagia (Marrosu et al., 2007). After VNS, improvement in the tremor and dysphagia was manifested over a period of 2 and 3 months, respectively. The head–neck postural tremor improved 67% on a disability rating scale. Water intake and "piecemeal" deglutition improved by 65% and 78%, respectively. Patients were followed up for 26 months during which the improvements persisted.

Postural cerebellar tremor represents a highly distressing condition in advanced MS and dysphagia is a life-threatening complication. Current treatments often fail to improve these. Hence, the investigation of VNS therapy as a possible treatment should be considered.

Eating Disorders and VNS

Bulimia nervosa is an eating disorder characterized by the intake of large amounts of food over a defined period with a loss of control over the consumption. This is followed by a compensatory behavior directed at eliminating the consumed calories, usually voluntary vomiting. Patients show a dampened satiety response to meal consumption (Kissileff et al., 1996). This satiety is under vagal control (Bray, 2000). In an attempt to dampen neural oscillations in the vagus, a trial was conducted with VNS therapy for 10 patients with severe unremitting bulimia (Faris et al, 2008). Patients were followed up during a 2-week baseline period and for 6 weeks on stable VNS settings. During these periods, binge eating and vomit episodes were recorded. Data from eight patients could be collected. The bulimic behaviors changed from ~28 episodes/wk to 1.4/wk at the end of the 6-week follow-up. Five of the eight patients achieved complete abstinence, which was accompanied by a normalization of their satiety response to a challenge meal.

Morbid obesity is defined as having a body mass index score of 40 or higher. This condition forms a serious health threat with increased risk for type II diabetes, obstructive sleep apnea, heart disease, and several major cancers. Currently, the only treatment options, which result in a lasting weight loss, are surgical procedures that restrict the stomach size or bypass parts of the intestine (Bult et al., 2008). Controlling the food intake through modulating the satiety using the vagal pathway was suggested. Burneo et al. (2002) analyzed the weight of 32 patients who had a VNS system implanted for intractable epilepsy. For 27 patients, a complete data set was available. None of the patients gained weight after VNS therapy. Eight patients lost weight significantly (>5%) of which five lost >10%.

In a phase I study, six patients with clinical criteria for morbid obesity surgery underwent implantation of bilateral vagus nerve stimulators (Roslin and Kurian, 2003). None of the patients reported significant discomfort. One patient was >400 pounds at baseline and lost >90 pounds, an effect that lasted. A second patient lost 40 pounds, but had to leave the study due to pregnancy. Two patients lost ~10% of their weight and then saturated. In the final two patients, no effects were observed.

In 2006, the weight changes of 32 patients with intractable epilepsy were analyzed retrospectively over a period of 2 years (Koren and Holmes, 2006). The authors found no significant average weight change in the group of patients during the 2-year study period. Similar results were found by another retrospective analysis of 31 patients of which the weight information was available for 22 patients (Abubakr and Wambacq, 2008). These patients were also treated for intractable epilepsy. Four patients lost weight ranging from 11% to 28%, whereas four patients gained weight in the range of 8% to 15%.

In a recent study, the weight of 14 patients, receiving VNS therapy for treatment-resistant depression, was followed up till 1 year (Pardo et al., 2007). The average weight loss was 7 kg, which was associated with a drop in the body mass index of 2 kg/m^2. Interestingly, the loss in weight was positively correlated with the body mass index value at baseline, meaning that the more severe the obesity, the greater the weight loss. The weight loss was not correlated with the reduction in depression ratings.

Bodenlos et al. (2007) showed that VNS acutely affected food cravings in people with the VNS system for depression. This was especially the case for sweets. The food craving for sweets either

increased or decreased on activation of the VNS system. Increase in craving was associated with low VNS device on time, lower levels of output current, and lower body mass index values. Decreased craving for sweets correlated with increased on time, higher levels of depression, and higher levels of emotional eating with depression.

Given the increasing prevalence of eating disorders and the limited treatment options, additional therapies are welcome. However, the available apparently conflicting data do not unambiguously add VNS therapy to the existing treatment options yet. But further research is warranted.

Mechanism of VNS

Although the exact mechanism through which VNS therapy displays its various effects is not known, many pieces of the puzzle have been found (Henry, 2002; Nemeroff et al., 2006). The antiepileptic effects have been attributed to several processes. First, VNS causes an increased synaptic activity in the thalamus and thalamocortical projection pathways, which would result in an increased arousal and possibly a decreased synchrony of synaptic activities between and within cortical regions. Second, VNS leads to intermittently increased synaptic activities in components of the central autonomic system, such as the insula and the hypothalamus. Third, there is transiently decreased synaptic activity in components of the limbic system, such as the amygdala and the hippocampus. And finally, VNS therapy results in intermittently increased release of norepinephrine and serotonin over widespread cerebral regions. All these regions are either innervated directly by the vagus or indirectly through the nucleus tractus solitarius (NTS; Fig. 2). The fibers of the left vagus nerve project bilaterally to the NTS. The central role of the NTS in the antiepileptic effects of VNS is demonstrated by the experiments of Walker et al. (1999) in which a decrease in NTS activity, by means of an increase in γ-aminobutyric acid or a decrease in glutamate, had an anticonvulsant effect. The locus coeruleus also has a key role, which is directly connected to the NTS, as was shown by Krahl et al. (1998). In rats, lesioning of this area prevented VNS to control seizures. Activation of the locus coeruleus inhibited the development of kindling-induced seizures (Jimenez-Rivera et al., 1987).

In a recent study, it was shown that acute limbic hyperperfusion and chronic thalamic hypoperfusion correlate with positive clinical efficacy (Vonck et al., 2008). This creates an opportunity to identify responders before implantation.

For the antidepressant effects of VNS therapy, the direct stimulation of brain stem structures and indirect regulation of activity of neurons in limbic and cortical regions involved in mood regulation are held responsible. Using positron emission changes in regional cerebral blood flow in response to acute VNS were found in treatment-resistant depression patients. Increased regional cerebral blood flow was found in bilateral orbitofrontal cortex, bilateral anterior cingulate cortex, and right parietal area on acute activation (Conway et al., 2006). These regions are both associated with depression and the afferent pathways of the vagus nerve. After 4 weeks of VNS therapy, decreased blood flow was found in the amygdala, left hippocampus, left cingulate cortex, bilateral ventral anterior cingulate, right thalamus, and brain stem, and increased regional cerebral blood flow was found in the middle frontal gyrus (Zobel et al., 2005). This pattern shares features with changes on regional cerebral blood flow seen as a result of pharmacologic treatment of depression.

Dorr and Debonnel (2006) showed that both serotonergic neurons from dorsal raphe nucleus and noradrenergic neurons from the locus coeruleus in rats increased firing rates over a period of weeks during VNS treatment. Both these neurotransmitters are involved in the pathophysiology of mood disorders. Using transcranial magnetic stimulation, Bajbouj et al. (2007)

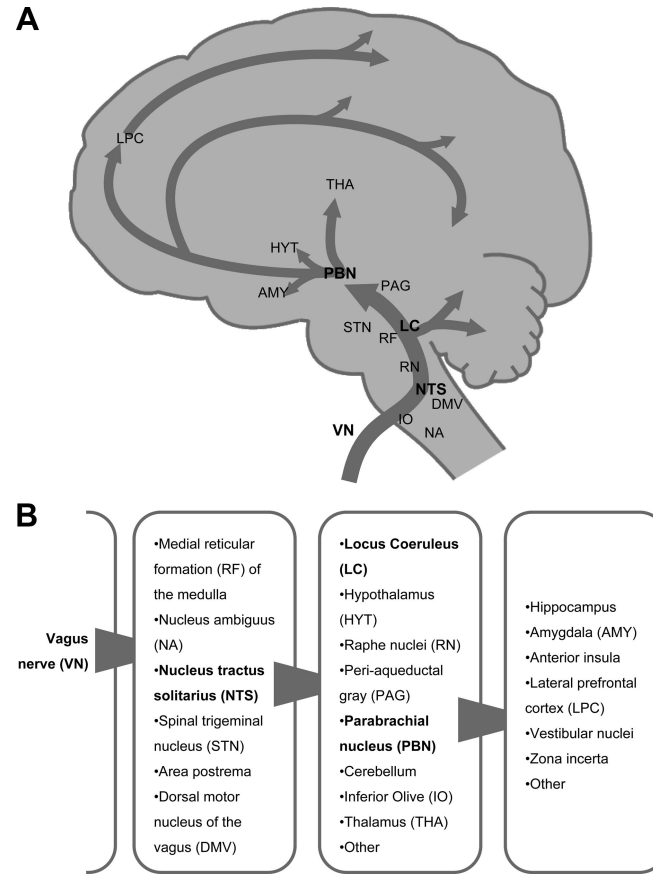

FIGURE 2. Anatomic overview of the projections of the vagus nerve. (**A**) Schematic representation of the brain regions innervated directly or indirectly by the vagus nerve. Abbreviations are taken from panel (**B**), a scheme with sequential projections of the vagus nerve.

showed that the intracortical inhibition in the motor cortex increased after 10 weeks of VNS. The same group showed earlier a correlation between depression severity and intracortical inhibition (Bajbouj et al., 2006).

Even though effects of VNS therapy on other pathologic conditions are yet to be confirmed, some things can be said about their presumed mechanism.

The pathophysiology of migraine remains incompletely understood (Rogawski, 2008). It is believed that a neuronal hyperexcitability is at the onset of the disorder, and that the process driving the pathogenesis of the migraine attack may be located in the brainstem (Spierings, 2003).

For pain in general, the vagus nerve plays a role (Randich and Gebhart, 1992). In patients with complete spinal cord injury, pain thresholds go up after vaginocervical self-stimulation, whereas tactile thresholds do not change (Komisaruk and Sansone, 2003). The complete spinal cord injury ensured that the effect was vagus nerve mediated. Electrical VNS in rats has been shown to attenuate heat- and formalin-induced pain (Bohotin et al., 2003). In a study in which visceral pain was induced in rats through graded colorectal distension, subdiaphragmatic electric vagal stimulation reduced pain (Chen et al., 2008). The authors showed that this effect only occurred through stimulation of Aδ-fibers and was absent when C-fibers were stimulated. This is in concordance with therapeutic

stimulation in humans in whom only Aδ-fibers are believed to be activated (Krahl et al., 2001).

Alzheimer's disease is commonly accompanied by degeneration of the locus coeruleus (Haglund et al., 2006), which is indirectly innervated by the vagus nerve. The subsequent reduced levels of norepinephrine increase plague burden. Norepinephrine has been shown to be essential in maintaining adequate beta amyloid clearance (Kalinin et al., 2007).

The alleged improvements in postural cerebellar tremor in MS may be attributed to the role of the inferior olive. The inferior olive gets input from the NTS (Tong et al., 1991). VNS may be down regulating the inferior olive-cerebellar microcircuit. Increased inferior olive firing has been associated with cerebellar tremor in an animal model (Krahl et al., 2004).

In eating disorders, the vagus nerve plays a central role, forming the main link between the gut and the brain. Women with bulimia have an impaired ability to think satiated during a meal. Most likely, there is a dysregulation of short-term, preabsorptive satiety mechanisms. These mechanisms involve, besides hormones released from intestinal cells acting on cortico-limbic brain structures, activation of vagal afferents (Berthoud, 2008). The satiety response is likely to be programmed in the brainstem, because decerebrate rats display normal meal-ending behavior (Grill and Kaplan, 2002).

The diseases that seem to benefit from VNS therapy seem unrelated at first sight. However, there is a remarkable comorbidity. Depression is common in intractable epilepsy patients and often depression precedes the onset of epilepsy, indicating a bidirectional relation (Kanner, 2008). The prevalence of migraine in patients suffering from bulimia nervosa is >80%, compared with 12.5% in the normal population, with the onset of migraine starting before or at the same time as the eating disorder (Ostuzzi et al., 2008). Migraine patients are more than twice as likely to have epilepsy and vice versa (Bigal et al., 2003). A recent meta-analysis shows that obesity increases the risk of Alzheimer's disease (Beydoun et al., 2008). The relation is not understood, but stands even if controlled for sociodemographic, lifestyle, and health-related comorbid factors. In up to 50% of patients with Alzheimer's disease, depression is comorbid and a history of depression, particularly an early onset, increases the risk for Alzheimer's disease (Geerlings et al., 2008). A high percentage of people suffering with Tourette's syndrome also have depression (Robertson, 2006) and have a significant higher frequency of migraine headaches (Kwak et al., 2003). Tourette's syndrome (TS) is a neurologic disorder characterized by motor and phonic tics. Two cases have been described with TS and VNS therapy. The first case concerned a 30-year-old patient, with TS from the age of 3 years and complex partial seizures from the age of 8 years (Diamond et al., 2006). Two days after the onset of VNS therapy, the patient reported improvement in both phonic and motor tics. These improvements were confirmed through video observations by a "blind" rater. A second case was described by Sperling et al. (2008). A 63-year-old man with TS since the age of 16 years, who developed recurrent major depression at the age of 25 years, was treated with VNS therapy. The patient's depression rating decreased after 6 months. Nine months after onset, the patient reported a marked decrease in his symptoms related to TS. The improvement was confirmed by neurologic examination. During the 15-month follow-up, the improvements persisted. The authors suggested that activation of the locus coeruleus and the dorsolateral prefrontal cortex would be involved in the efficacy of VNS in TS.

In all disorders described, the vagus nerve and/or one of the areas innervated by it play a role (Fig. 2). The vagus nerve is a mainly afferent (80%) cranial nerve (Foley and Dubois, 1937). The vagus nerve projects ipsilaterally on the dorsal motor nucleus of the vagus, the spinal trigeminal nucleus, the area postrema, the nucleus ambiguous, and the reticular formation. However, the majority projects bilaterally to the NTS. Subsequent projections from the NTS go to the parabrachial nucleus, the periaqueductal gray, the vermis and the inferior portions of the cerebellum, the locus coeruleus, the raphe nuclei, and other nuclei of the dorsal medullary complex. The parabrachial nucleus, on its turn, relays information to the thalamus, hypothalamus, hippocampus, amygdala, anterior insula, and the lateral prefrontal cortex. With such a list of destinations, all within reach by several synaptic connections, the vagus nerve can affect a broad range of basic brain functions. These include serving as a switching station (e.g., thalamus) and the emotional evaluation of information (limbic system).

The success of VNS may be that instead of electrically stimulating the areas of interest, the stimulation is indirect. The vagus nerve itself has a transmitting but not a processing function, which may be the reason that the vagus nerve does not adapt or desensitizes to the electrical stimulation provided by the VNS system. The vagus nerve translates the "unnatural" electrical block pulses into "natural" action potentials. As a result, areas of interest are functionally modulated without damage, nor is the stimulation locally hampered by fibrous tissue.

CONCLUSION

VNS therapy has been shown extensively to be useful in the treatment of therapy-resistant epilepsy. For the application of VNS therapy in treatment-resistant depression, much evidence is available, yet a long-term randomized controlled study that demonstrates unequivocally a benefit for these patients is lacking. In addition to these Food and Drug Administration-approved indications, several other possible applications of VNS therapy are under investigation. Although this concerns different disorders at first sight, they all do share common features, including a prominent role for the vagus nerve or one of its projections. The variety in possible indications for VNS therapy reflects the broad range of functions of the vagus nerve and do emphasize the need for further research on the role of modulation of the vagal nerve in the treatment of various diseases.

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