The Mechanism of Action of Vagus Nerve Stimulation Therapy

a report by
Kristl Vonck *and* **Paul Boon**

Reference Centre for Refractory Epilepsy, Laboratory for Clinical and Experimental Neurophysiology, Department of Neurology, Ghent University Hospital
DOI:10.17925/ENR.2008.03.02.97

The inability to adequately treat all patients with refractory epilepsy provides a continuous impetus to investigate novel forms of treatment. Neurostimulation is an emerging treatment for neurological diseases. Electrical pulses are administered directly to, or in the surrounding area of, nervous tissue in order to manipulate a pathological substrate and to achieve a symptomatic or even curative therapeutic effect. Electrical stimulation of the 10th cranial nerve, or vagus nerve stimulation (VNS), is an extracranial form of neurostimulation that was developed in the 1980s.[1] In the past decade it has become a valuable option in the therapeutic armamentarium for patients with refractory epilepsy and it is currently routinely available in epilepsy centres worldwide. Through an implanted device and electrode, electrical pulses are administered to the afferent fibres of the left vagus nerve in the neck. It is indicated in patients with refractory epilepsy who are unsuitable candidates for epilepsy surgery or who have had insufficient benefit from such a treatment.

Since the first human implant of the VNS Therapy™ device in 1989, over 50,000 patients have been treated with VNS worldwide. As with many antiepileptic treatments, the clinical application of VNS preceded the elucidation of its mechanism of action (MOA). Following a limited number of animal experiments in dogs and monkeys investigating safety and efficacy, the first human trial was carried out.[2] One-third of patients with refractory epilepsy treated with VNS were responders and 7–8% became seizure-free.[3] It remains unclear what type of epileptic seizures or syndromes respond optimally to VNS. Elucidation of the MOA may improve clinical outcome, as it may provide strategies for the optimisation of stimulation parameters and the identification of suitable VNS candidates.

The Anatomical Basis of Vagus Nerve Stimulation

The vagus nerve is a mixed cranial nerve that consists of ~80% afferent fibres originating from the heart, aorta, lungs and gastrointestinal tract and ~20% efferent fibres that provide parasympathetic innervation of these structures and also innervate the voluntary striated muscles of the larynx and pharynx.[4–6] Somata of the efferent fibres are located in the dorsal motor nucleus and nucleus ambiguus. Afferent fibres have their origin in the nodose ganglion and primarily project to the nucleus of the solitary tract. At the cervical level the vagus nerve mainly consists of small-diameter unmyelinated C-fibres (65–80%), with a smaller portion of intermediate-diameter myelinated B-fibres and large-diameter myelinated A-fibres. The nucleus of the solitary tract has widespread projections to numerous areas in the forebrain, as well as the brainstem, including important areas for epileptogenesis such as the amygdala and thalamus. There are direct neural projections into the raphe nucleus, which is the major source of serotonergic neurons, and indirect projections to the locus coeruleus and A5 nuclei, which contain noradrenegic neurons. Finally, there are numerous diffuse cortical connections.

The diffuse pathways of the vagus nerve mediate important visceral reflexes such as coughing, vomiting, swallowing and control of blood pressure and heart rate. Heart rate is mostly influenced by the right vagus nerve, which has dense projections primarily to the atria of the heart.[7]

Relatively few specific functions of the vagus nerve have been well characterised. The vagus nerve is often considered to be protective, defensive and relaxing. This primary function is exemplified by the lateral line system in fish, the early precedent of the autonomic nervous system.[8] The control of homeostatic functions by the central nervous system in these earlier life forms was limited to the escape and avoidance of perturbing stimuli or suboptimal conditions. Its complex anatomical distribution has earned the vagus nerve its name, as 'vagus' is the Latin word for wanderer. These two facts together inspired Andrews and Lawes to suggest the name 'great wandering protector'.[8]

How to Investigate the Mechanism of Action of Vagus Nerve Stimulation

The basic hypothesis of the MOA was based on the knowledge that the 10th cranial nerve afferents have numerous projections within the central nervous system and that, in this way, action potentials generated in vagal afferents have the potential to affect the entire organism.[9] To date, the precise MOA of VNS and how it suppresses seizures remains to be elucidated. Crucial questions with regard to the MOA of VNS occur at different levels.

Nerve Fibres, Central Nervous System Structures and Neurotransmitters

VNS aims to induce action potentials within the different types of fibres that constitute the nerve at the cervical level. The question remains: which fibres are responsible and/or necessary for its seizure-suppressing effect? Unidirectional stimulation, activating afferent vagal fibres, is preferred, as epilepsy is considered a disease with cortical origin, and efferent stimulation may cause adverse effects. The next step is to identify central nervous system structures located on the anatomical pathways from the cervical part of the vagus nerve up to the cortex that play a functional role in the MOA of VNS. These could be central gateway or pacemaker function structures such as

Kristl Vonck is an Associate Professor in Neurology at Ghent University Hospital. Her research fields include neurostimulation, stem cells and local drug delivery. She has published 120 abstracts in international peer-reviewed journals, 85 manuscripts, five book chapters and 90 presentations. Professor Vonck received her medical training at Guy's Hospital, London and Yale University School of Medicine.

E: kristl.vonck@ugent.be

the thalamus, or more specific targets involved in the pathophysiology of epilepsy such as the limbic system, or a combination of both. Another issue concerns the identification of the potential involvement of specific neurotransmitters. The intracranial effect of VNS may be based on local or regional gamma aminobutyric acid (GABA) increases or glutamate and aspartate decreases, or may involve other neurotransmitters that have been shown in the past to have a seizure threshold-regulating role, such as serotonine and norepinephrine.[10]

Antiseizure, Antiepileptic and Antiepileptogenic Treatments

When considering the efficacy of a given treatment in epilepsy, a certain hierarchical profile of the treatment can be distinguished. A treatment can have pure antiseizure effects, meaning that it can abort seizures. To confirm such an effect the treatment is most often administered during an animal experiment in which the animals are injected with a proconvulsant compound followed by the administration of the treatment under investigation. A treatment may provide a true preventative or so-called antiepileptic effect. Antiepileptic efficacy implies that a treatment can prevent seizures, as the main characteristic of the disease, namely the unexpected recurrence of seizures, is prevented from happening. A treatment can also have an antiepileptogenic effect. This implies that the treatment reverses the development of a pathological process that may have evolved over a long period of time. Such a treatment is clearly protective and may even be used for other neuroprotective purposes.

Research Investigating the Mechanism of Action of Vagus Nerve Stimulation

Research directed towards investigating the antiseizure, antiepileptic and potential antiepileptogenic properties of VNS, as well as towards the identification of involved fibres, intracranial structures and neurotransmitter systems, has been carried out. Animal experiments and research in humans treated with VNS have comprised electrophysiological studies (electroencephalogram [EEG], electromyogram and evoked potential), functional anatomical brain imaging studies (positron emission tomography, single proton emission computed tomography [SPECT], functional magnetic resonance imaging, c-fos and densitometry), neuropsychological studies and behavioural studies. Also from the extensive clinical experience with VNS, interesting clues concerning the MOA of VNS have arisen. More recently, the role of the vagus nerve in the immune system has been investigated.

Nerve Fibres, Central Nervous System Structures and Neurotransmitters

From the extensive body of research on the MOA, it is now assumed that effective stimulation in humans is primarily mediated by afferent vagal A- and B-fibres.[11,12] Unilateral stimulation affects both cerebral hemispheres, as shown in several functional imaging studies.[13–15] Brainstem and intracranial structures have been identified and include the locus coeruleus, the nucleus of the solitary tract, the thalamus and limbic structures.[16–19] Neurotransmitters playing a role may involve the major inhibitory neurotransmitter GABA, but also serotoninergic and adrenergic systems.[20,21] More recently, Neese et al. found that VNS following experimental brain injury in rats protects cortical GABAergic cells from death.[22] A SPECT study in humans before and after one year of VNS showed a normalisation of $GABA_A$ receptor density in the individuals with a clear therapeutic response to VNS.[23] Follesa et al. showed an increase of norepinephrine concentration in the prefrontal cortex of the rat brain after acute VNS.[24] An increased norepinephrine concentration after VNS has also been measured in the hippocampus[25] and amygdala.[26] Currently, VNS as a neuroimmunomodulatory treatment is being explored. As the vagus nerve plays a critical role in the signalisation and modulation of inflammatory processes, the so-called anti-inflammatory pathway, this could represent a new modality in the MOA of VNS for epilepsy.[27,28] Recent experiments have shown that VNS significantly increases cortisol levels in freely moving rats.[29]

Antiseizure, Antiepileptic and Antiepileptogenic Treatments

Early animal experiments in acute seizure models suggested an antiseizure effect of VNS. McLachlan found that applying VNS at the beginning of a pentylenetetrazole (PTZ)-induced seizure significantly shortened the seizure.[30] Woodbury and Woodbury described the beneficial effect of VNS in preventing or reducing PTZ-induced clonic seizures and electrically induced tonic–clonic seizures in rats.[31] Zabara found that VNS interrupts or abolishes motor seizures in canines induced by strychnine.[32] In our own group, VNS significantly increased the seizure threshold for focal motor seizures in the cortical stimulation model.[33] Also in the literature on humans, there is clear evidence of an acute abortive effect of VNS. The magnet feature allows a patient to terminate an upcoming seizure.[34] In addition, a few case reports describe the use of VNS for refractory status epilepticus in paediatric and adult patients.[35,36]

However, in the clinical trials with VNS, many patients did not regularly self-trigger the device at the time of a seizure and still showed good response to VNS. In addition, VNS is administered in an intermittent way, and it appears that seizures occurring during the VNS off-time are also affected. This intermittent method of stimulation is insufficient to explain the reduction of seizures on the basis of abortive effects alone and suggests a true preventative or so-called antiepileptic effect of VNS. The fact that VNS influences seizures at a time when stimulation is in the off-mode has also been shown in many animal and human experiments. In 1985 Zabara reported that seizure control was extended well beyond the end of the stimulation period. Stimulation for one minute could produce seizure suppression for five minutes in canines.[32,37] Naritoku and Mikels showed that VNS pre-treatment during one and 60 minutes, prior to administration of the seizure-triggering stimulation, significantly reduced the duration of behavioural seizures and the duration of afterdischarges in amygdala kindled rats.[38] In a study by Takaya et al. VNS was discontinued before induction of PTZ seizures that were significantly shortened in duration.[39] In addition, repetition of stimuli increased VNS efficacy, suggesting that efficacy of intermittent stimulation improves with long-term use. Zagon and Kemeny found that VNS-induced slow hyperpolarisation in the parietal cortex of the rat outlasted a 20-second VNS train by 15 seconds.[11] McLachlan found that interictal spike frequency was significantly decreased or abolished after 20 seconds of VNS in rats for a variable duration, usually around 60 seconds to three minutes after stimulation discontinuation.[40] Recent data in human EEG studies show a decrease in interictal epileptiform discharges, both in an acute form and after long-term follow-up.[41,42]

The fact that seizures reoccur after the end of battery life has been reached is a strong argument against VNS having an antiepileptogenic effect. However, as progress in the development of more relevant animal models for epilepsy has been made, the antiepileptogenic potential of neurostimulation in general is being fully explored, and some promising results have been reported, e.g. in the kindling model.[38,43] In literature on

VAGUS NERVE STIMULATION VNS THERAPY™

Enabling your patients to enjoy life

Just like everyone else, patients with difficult-to-treat epilepsy want to enjoy their lives. However, it is inevitably difficult to provide help to patients who have tried out a number of different epilepsy treatments with little or no success.

VNS Therapy has been developed for both adults and children and is applied through a small device. This non-pharmacological treatment is an adjunctive therapy to be used with drugs, and this means that your patients' medication intake might be reduced. In turn, this could lead to a reduction in the side effects associated with the drugs they are taking.

VNS Therapy could help your patients to experience reductions in the frequency and intensity of their seizures. Furthermore, your patients may feel improvements in terms of their mood, alertness and sense of control.

In essence, the aim of VNS Therapy is to help your patients to experience increased confidence, independence and enjoyment of life.

The reality is that there are a limited number of options in dealing with difficult-to-treat epilepsy. By choosing VNS Therapy, you might well find the option that will best suit your patients.

EUROPEAN INDICATION FOR USE:
The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalisation) or generalised seizures, which are refractory to antiepileptic medications.

Cyberonics Europe S.A./N.V.
Belgicastraat 9, 1930 Zaventem, Belgium
Tel. +32 2 720 95 93, Fax +32 2 720 60 53
www.VNSTherapy.eu

REFERENCES: Morris G.L. et al. *Neurology* 1999; 53(7):1731-1735 • Tatum W.O. et al. *Neurology* 2001; 56(4):561-563 • Harden C.L. et al. *Epilepsy & Behavior* 2000; 1:93-99 • Elger G. et al. *Epilepsy Research* 2000; 42:203-210 • VNS Therapy Patients Registry, April 25, 2003. Data on file, Cyberonics, Inc. Houston, Tex. • Rychlicki F. et al. *Seizure* 2006; 15(7):483-490 • Matsuura M. *Psychiatry and Clinical Neurosciences* 2000; 54(2):249-253 • Henry T. R. *Neurology* 2002; 59(Suppl 4): S3-S14 • Fromes G.A. et al. Epilepsia 2000; 41(7):117

Brief Summary[1] of Safety Information for the VNS Therapy™ System [Epilepsy and Depression Indications] (March 2007)

1. INTENDED USE / INDICATIONS Epilepsy (Non-US) — The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalized seizures that are refractory to antiepileptic medications. Depression (Non-US) — The VNS Therapy System is indicated for the treatment of chronic or recurrent depression in patients that are in a treatment-resistant or treatment-intolerant depressive episode. 2. CONTRAINDICATIONS Vagotomy — The VNS Therapy System cannot be used in patients after a bilateral or left cervical vagotomy. Diathermy — Do not use short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy on patients implanted with a VNS Therapy System. Diagnostic ultrasound is not included in this contraindication. 3. WARNINGS — GENERAL Physicians should inform patients about all potential risks and adverse events discussed in the physician's manuals. This document is not intended to serve as a substitute for the complete physician's manuals. The safety and efficacy of the VNS Therapy System have not been established for uses outside the "Intended Use/Indications" section of the physician's manuals. The safety and effectiveness of the VNS Therapy System in patients with predisposed dysfunction of cardiac conduction systems (re-entry pathway) have not been established. Post-implant electrocardiograms and Holter monitoring are recommended if clinically indicated. Postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. It is important to follow recommended implantation procedures and intraoperative product testing described in the Implantation Procedure part of the physician's manuals. During the intraoperative System Diagnostics (Lead Test), infrequent incidents of bradycardia and/or asystole have occurred. If asystole, severe bradycardia (heart rate <40 bpm), or a clinically significant change in heart rate is encountered during a System Diagnostics (Lead Test) or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS). Difficulty swallowing (dysphagia) may occur with active stimulation, and aspiration may result from the increased swallowing difficulties. Patients with pre-existing swallowing difficulties are at greater risk for aspiration. Dyspnea (shortness of breath) may occur with active VNS Therapy. Any patient with underlying pulmonary disease or insufficiency such as chronic obstructive pulmonary disease or asthma may be at increased risk for dyspnea. Patients with obstructive sleep apnea (OSA) may have an increase in apneic events during stimulation. Lowering stimulus frequency or prolonging "OFF" time may prevent exacerbation of OSA. Vagus nerve stimulation may also cause new onset sleep apnea in patients who have not previously been diagnosed with this disorder. Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause nerve damage. Patients should be instructed to use the Magnet to stop stimulation if they suspect a malfunction, and then to contact their physician immediately for further evaluation. Patients with the VNS Therapy System or any part of the VNS Therapy System implanted should not have full body MRI. Excessive stimulation at an excess duty cycle (that is, one that occurs when "ON" time is greater than "OFF" time) has resulted in degenerative nerve damage in laboratory animals. Patients who manipulate the Pulse Generator and Lead through the skin (Twiddler's Syndrome) may damage or disconnect the Lead from the Pulse Generator and/or possibly cause damage to the vagus nerve. 4. WARNINGS — EPILEPSY The VNS Therapy System should only be prescribed and monitored by physicians who have specific training and expertise in the management of seizures and the use of this device. It should only be implanted by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device. The VNS Therapy System is not curative. Physicians should warn patients that the VNS Therapy System is not a cure for epilepsy and that since seizures may occur unexpectedly, patients should consult with a physician before engaging in unsupervised activities, such as driving, swimming, and bathing, and in strenuous sports that could harm them or others. Sudden unexplained death in epilepsy (SUDEP): Through August 1996, 10 sudden and unexplained deaths (definite, probable, and possible) were recorded among the 1,000 patients implanted and treated with the VNS Therapy device. During this period, these patients had accumulated 2,017 patient-years of exposure. Some of these deaths could represent seizure-related deaths in which the seizure was not observed, at night, for example. This number represents an incidence of 5.0 definite, probable, and possible SUDEP deaths per 1,000 patient-years. Although this rate exceeds that expected in a healthy (nonepileptic) population matched for age and sex, it is within the range of estimates for epilepsy patients not receiving vagus nerve stimulation, ranging from 1.3 SUDEP deaths for the general population of patients with epilepsy, to 3.5 (for definite and probable) for a recently studied antiepileptic drug (AED) clinical trial population similar to the VNS Therapy System clinical cohort, to 9.3 for patients with medically intractable epilepsy who were epilepsy surgery candidates. 5. WARNINGS — DEPRESSION This device is a permanent implant. It is only to be used in patients with severe depression who are unresponsive to standard psychiatric management. It should only be prescribed and monitored by physicians who have specific training and expertise in the management of treatment-resistant depression and the use of this device. It should only be implanted by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device. Physicians should warn patients that VNS Therapy has not been determined to be a cure for depression. Patients being treated with adjunctive VNS Therapy should be observed closely for clinical worsening and suicidality, especially at the time of VNS Therapy stimulation parameter changes or drug or drug dose changes. Excessive stimulation: Note: Use of the Magnet to activate stimulation is not recommended for patients with depression. 6. PRECAUTIONS — GENERAL Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy physician's manuals. Prescribing physicians should be experienced in the diagnosis and treatment of depression or epilepsy and should be familiar with the programming and use of the VNS Therapy System. Physicians who implant the VNS Therapy System should be experienced performing surgery in the carotid sheath and should be trained in the surgical technique relating to implantation of the VNS Therapy System. The safety and effectiveness of the VNS Therapy System have not been established for use during pregnancy. VNS should be used during pregnancy only if clearly needed. The VNS Therapy System is indicated for use only in stimulating the left vagus nerve in the neck area inside the carotid sheath. The VNS Therapy System is indicated for use only in stimulating the left vagus nerve below where the superior and inferior cervical cardiac branches separate from the vagus nerve. It is important to follow infection control procedures. Infections related to any implanted device are difficult to treat and may require that the device be explanted. The patient should be given antibiotics preoperatively. The surgeon should ensure that all instruments are sterile prior to the procedure. The VNS Therapy System may affect the operation of other implanted devices, such as cardiac pacemakers and implanted defibrillators. Possible effects include sensing problems and inappropriate device responses. If the patient requires concurrent implantable pacemaker, defibrillatory therapy or other types of stimulators, careful programming of each system may be necessary to optimize the patient's benefit from each device. Reversal of Lead polarity has been associated with an increased chance of bradycardia in animal studies. It is important that the electrodes are attached to the left vagus nerve in the correct orientation. It is also important to make sure that Leads with dual connector pins are correctly inserted (white marker band to + connection) into the Pulse Generator's Lead receptacles. The patient can use a neck brace for the first week to help ensure proper Lead stabilization. Do not program the VNS Therapy System to an "ON" or periodic stimulation treatment for at least 14 days after the initial or replacement implantation. Do not use frequencies of 5 Hz or below for long-term stimulation. Resetting the Pulse Generator turns the device OFF (output current = 0.0 mA), and all device history information is lost. Patients who smoke may have an increased risk of laryngeal irritation. 7. ENVIRONMENTAL AND MEDICAL THERAPY HAZARDS Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. If a Pulse Generator ceases operation while in the presence of electromagnetic interference (EMI), moving away from the source may allow it to return to its normal mode of operation. VNS Therapy System operation should always be checked by performing device diagnostics after any of the procedures mentioned in the physician's manuals. For clear imaging, patients may need to be specially positioned for mammography procedures, because of the location of the Pulse Generator in the chest. Therapeutic radiation may damage the Pulse Generator's circuitry, although no testing has been done to date and no definite information on radiation effects is available. Sources of such radiation include therapeutic radiation, cobalt machines, and linear accelerators. The radiation effect is cumulative, with the total dosage determining the extent of damage. The effects of exposure to such radiation can range from a temporary disturbance to permanent damage, and may not be detectable immediately. External defibrillation may damage the Pulse Generator. Use of electrosurgery [electrocautery or radio frequency (RF) ablation devices] may damage the Pulse Generator. Magnetic resonance imaging (MRI) should not be performed with a magnetic resonance body coil in the transmit mode. The heat induced in the Lead by an MRI body scan can cause injury. Additionally, in vitro tests have shown that an intact Lead without an implanted Pulse Generator presents substantially the same hazards as a full VNS Therapy System. If an MRI should be done, use only a transmit-and-receive type of head coil. MRI compatibility was demonstrated using 1.5T General Electric Signa and 3.0T Philips MR systems. Use caution when other MR systems are used, since adverse events may occur because of different magnetic field distributions. Consider other imaging modalities when appropriate. Procedures in which the radio frequency (RF) is transmitted by the body coil should not be done on a patient who has the VNS Therapy System. Thus, protocols must not be used that utilize local coils that are RF receive-only, with RF-transmit performed by the body coil. Note that some RF head coils are receive-only, and that most other local coils, such as knee and spinal coils, are also RF-receive only. These coils must not be used in patients with the VNS Therapy System. See MRI with the VNS Therapy System (Non-U.S. version) for details. Extracorporeal shockwave lithotripsy may damage the Pulse Generator. If therapeutic ultrasound therapy is required, avoid positioning the area of the body where the Pulse Generator is implanted in the water bath or in any other position that would expose it to ultrasound therapy. If that positioning cannot be avoided, program the Pulse Generator output to 0 mA for the treatment, and then after therapy, reprogram the Pulse Generator to the original parameters. If the patient receives medical treatment for which electric current is passed through the body (such as from a TENS unit), either the Pulse Generator should be set to 0 mA or function of the Pulse Generator should be monitored during initial stages of treatment. Routine therapeutic ultrasound could damage the Pulse Generator and may be inadvertently concentrated by the device, causing harm to the patient. For complete information related to home occupational environments, cellular phones, other environmental hazards, other devices, and ECG monitors, refer to the physician's manuals. 8. ADVERSE EVENTS — EPILEPSY Adverse events reported during clinical studies as statistically significant are listed below in alphabetical order: ataxia (loss of the ability to coordinate muscular movement); dyspepsia (indigestion); dyspnea (difficulty breathing, shortness of breath); hypesthesia (impaired sense of touch); increased coughing; infection; insomnia (inability to sleep); laryngismus (throat, larynx spasms); nausea; pain; paresthesia (prickling of the skin); pharyngitis (inflammation of the pharynx, throat); voice alteration (hoarseness); vomiting. 9. ADVERSE EVENTS — DEPRESSION Implant-related adverse events reported during the pivotal study in ≥ 5% of patients are listed in order of decreasing occurrence: incision pain, voice alteration, incision site reaction, device site pain, device site reaction, pharyngitis, dysphagia, hypesthesia, dyspnea, nausea, headache, neck pain, pain, paresthesia, and cough increased. Stimulation-related adverse events reported during the acute sham-controlled study by ≥ 5% of VNS Therapy-treated patients are (in order of decreasing occurrence): voice alteration, cough increased, dyspnea, neck pain, dysphagia, laryngismus, paresthesia, pharyngitis, nausea, and incision pain.

Cyberonics, Inc., 100 Cyberonics Boulevard, Houston, Texas 77058 USA,
Tel. 281-228-7200 / 800-332-1375, Fax 281-218-9332
Cyberonics Europe, S.A./N.V., Belgicastraat 9, 1930 Zaventem, Belgium,
Tel. +32 2 720 95 93, Fax +32 2 720 60 53
www.VNSTherapy.com

26-0006-8800/2

[1] The information contained in this Brief Summary for Physicians represents partial excerpts of important prescribing information taken from the physician's manuals. (Copies of VNS Therapy physician's and patient's manuals are posted at www.VNSTherapy.com/manuals.) The information is not intended to serve as a substitute for a complete and thorough understanding of the material presented in all of the physician's manuals for the VNS Therapy System and its component parts nor does this information represent full disclosure of all pertinent information concerning the use of this product, potential safety complications, or efficacy outcomes.

PhysAdGenA4B508-11-1000-EC

humans, one case report described long-lasting seizure control after explantation of the VNS device.[44]

The basis for the combined acute and more chronic effects of VNS most likely involves recruitment of different neuronal pathways and networks. The more chronic effects are thought to be a reflection of modulatory changes in subcortical site-specific synapses, with the potential to influence larger cortical areas. In the complex human brain these neuromodulatory processes require time to build up. Once installed, certain antiepileptic neural networks may be more easily recruited, e.g. by changing stimulation parameters that may then be titrated to the individual need of the patient. This raises hope for potential antiepileptogenic properties of VNS using long-term optimised stimulation parameters that may affect and potentially reverse pathological processes that have been installed over a long period of time. However, from a clinical point of view, as yet VNS cannot be considered a curative treatment.

Conclusion

Despite the fact that VNS is accepted in epilepsy centres worldwide as a valuable and reliable therapeutic option for patients who are unsuitable candidates for resective surgery, some specific issues remain to counteract its full therapeutic potential. On the basis of currently available data, the responder rate in patients treated with VNS is not substantially higher compared with recently marketed antiepileptic drugs. Efforts to decrease the number of non-responders may increasingly justify implantation with a device. To increase efficacy, research towards the elucidation of the MOA is crucial. In this way, rational stimulation paradigms may be investigated.

Animal research should be directed towards the identification of a useful model to evaluate the seizure-suppressing effects of VNS. The initial experiments investigating VNS in the PTZ and maximal electroshock model prove difficult to be reproduced even in the hands of experienced researchers. At Ghent University Hospital, VNS has shown efficacy in the motor cortex stimulation model.[45] The seizure threshold in this animal model significantly increases following one hour of VNS. This model can now be further applied to investigate the efficacy of different stimulation parameters. Apart from the acute seizure-suppressing effects of VNS, the more chronic and estimated neuromodulatory effects should be further investigated in the laboratory. Investigating VNS in a chronic setting requires efforts to investigate animals in chronic conditions with specifically designed electrodes that allow long-term treatment. At Ghent University Hospital, a chronic video-EEG monitoring unit with customised miniature vagus nerve electrodes has been designed for this purpose. Ongoing research is investigating the long-term effects of VNS in the rapid kindling model. The ultimate goal may be to investigate the efficacy of VNS in spontaneous seizures, as observed in status epilepticus models. Indications of involvement of specific neurotransmitters in VNS have been established. Further investigation of this topic may be performed using microdialysis techniques in different animal models.

Because of the variability of different phenotypes of epilepsy, it seems simplistic to assume that there are specific combinations of stimulation parameters that will optimally benefit all different types of epilepsy and all refractory individuals. Individually guided stimulation parameter titration may be a more successful avenue to follow. Research should therefore be directed towards finding non-invasive measures that can guide individual titration. Neurophysiological investigation, such as evoked potentials and EEG recording in particular, is encouraging.

Interesting research lines include the investigation of VNS efficacy in specific epilepsy conditions and in other neurological conditions. Case reports on the efficacy of VNS in status epilepticus are positive and require further prospective studies in larger patient groups.

From a more experimental view, VNS may be considered part of a closed-loop system whereby triggered VNS is performed on a more individualised basis. Research towards the development of transcutaneous systems may allow predictive factors to be identified for response before chronic implantation is performed.

With a rapidly evolving biomedical world, various neurostimulation modalities will be applied in patients with refractory epilepsy. Future studies will have to show the precise position of VNS in comparison with treatment such as deep brain stimulation and transcranial magnetic stimulation. ■

1. Ben-Menachem E, *Lancet Neurol*, 2003;1:477–82.
2. Uthman BM, Wilder BJ, Hammond EJ, Reid S, *Epilepsia*, 1990;31:S44–S50.
3. De Herdt V, Boon P, Ceulemans B, et al., *Eur J Paediatr Neurol*, 2007;11(5):261–9.
4. Paintal AS, *Physiology Review*, 1973;53:159–227.
5. Foley J, DuBois F, *J Comprehensive Neurol*, 1937;67:49–97.
6. Agostini E, Chinnock JE, Daly MD, Murray JG, *J Physiol*, 1957;135:182–205.
7. Saper C, Kibbe M, Hurley K, et al., *Circ Res*, 1990;67: 1345–54.
8. Andrews P, Lawes I, *Neuroanatomy and Physiology of Abdominal Vagal Afferents*, CRC Press, Boca Raton, FL 1992:221–48.
9. Berthoud H, Neuhuber WL, *Auton Neurosci*, 2000;85:1–17.
10. Proctor M, Gale K, *Epilepsy, the comprehensive CBD rom*, Lippincot Williams and Wilkins 1999:30.
11. Zagon A, Kemeny A, *Acta Neurol Scand*, 2008;41:1382–9.
12. Evans MS, Verma-Ahuja S, Naritoku DK, Espinosa JA, *Acta Neurol Scand*, 2004;110:232–8.
13. Henry TR, Bakay RAE, Votaw JR, et al., *Epilepsia*, 1998;39:983–90.
14. Van Laere K, Vonck K, Boon P, et al., *J Nucl Med*, 2002;43:733–44.
15. Vonck K, De Herdt V, Bosman T, et al., *Seizure*, 2008;17(8):699–706.
16. Naritoku D, Terry WJ, Helfert RH, *Epilepsy Res*, 1995;22:53–62.
17. Krahl SE, Clark KB, Smith DC, Browning RA, *Epilepsia*, 1998;39(7):709–14.
18. Osharina V, Bagaev V, Wallois F, Larnicol N, *Auton Neurosci*, 2006;126-127:72–80.
19. Cunningham JT, Mifflin SW, Gould GG, Frazer A, *Neuropsychopharmacology*, 2008;33(8)1884–95.
20. Hammond EJ, Uthman BM, Wilder BJ, et al., *Brain Res*, 1992;583:300–303.
21. Ben-Menachem E, Hamberger A, Hedner T, et al., *Epilepsy Res*, 1995;20:221–7.
22. Neese S, Sherill L, Tan A, et al., *Brain Res*, 2007;1128: 157–63.
23. Marrosu F, Serra A, Maleci A, et al., *Epilepsy Res*, 2003;55:59–70.
24. Follesa P, Biggio F, Gorini G, et al., *Brain Res*, 2007;1179:28–34.
25. Roosevelt RW, Smith DC, Clough RW, et al., *Brain Res*, 2006;1119(1):124–32.
26. Hassert DL, Miyashita T, Williams CL, *Behav Neurosci*, 2004;118(1):79–88.
27. Borovikova L, Ivanova S, Zhang M, et al., *Nature*, 2000;405:458–62.
28. Hosoi T, Okuma Y, Nomura Y, *Am J Pysiol Regulatory Integrative Comp Physiol*, 2000;279:141–7.
29. De Herdt V, Puimege L, De Waele J, et al., *J Neuroimmunol*, 2008; submitted.
30. McLachlan RS, *Epilepsia*, 1993;34(5):918–23.
31. Woodbury JW, Woodbury DM, *PACE*, 1991;14:94–107.
32. Zabara J, *Epilepsia*, 1992;33:1005–12.
33. De Herdt V, Dewaele J, Van Aken J, et al., *Epilepsia*, 2006;47(Suppl. 4):300–301.
34. Boon P, Vonck K, Van Walleghem P, et al., *J Clin Neurophysiol*, 2001;18:402–7.
35. Malik S, Hernandez A, *Epilepsia*, 2004;45(Suppl. 7):155–6.
36. De Herdt V, Waterschoot L, Vonck K, et al., *Eur J Paediatr Neurol*, 2008; Epub ahead of print.
37. Zabara J, *Electroencephalogr Clin Neurophysiol*, 1985:61:S162.
38. Naritoku DK, Mikels JA, *Epilepsia*, 1996;37(S5):75.
39. Takaya M, Terry WJ, Naritoku DK, *Epilepsia*, 1996;37:1111–16.
40. Mc Lachlan RS, *Ann Neurol*, 1992;32(2):245.
41. Santiago-Rodriguez E, Alonso-Vanegas M, Cardenas-Morales L, et al., *Seizure*, 2006;15:615–20.
42. Carrette E, De Herdt V, Manders J, et al., *Epilepsia*, 2007; abstract presented at the AES meeting 2007, Philadelphia.
43. Fernandez-Guardiola A, Martinez A, Valdes-Cruz A, et al., *Epilepsia*, 1999;40:822–9.
44. Labar D, Ponticello L, *Neurology*, 2003;61(12):1818.
45. De Herdt V, De Waele J, Van Aken J, et al., *Acta Neurol Scand*, 2008; submitted.