The Role of Vagus Nerve Stimulation in the Treatment of Epilepsy

a report by

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Following the first encouraging human trials in 1988,[1,2] several controlled studies have demonstrated the antiepileptic efficacy of adjunctive vagus nerve stimulation (VNS) in patients suffering from refractory seizures.[3–7] Accordingly, VNS was approved in Europe in 1994 as an antiepileptic treatment for patients with generalised or focal drug-resistant epilepsy. In 1997, the US Food and Drug Administration (FDA) approved VNS as an adjunctive antiepileptic treatment for patients over 12 years of age suffering from drug-resistant partial epilepsy.

At present, more than 50,000 patients from 24 countries have been treated with VNS, a widely used non-pharmacological treatment for epilepsy. The antiepileptic efficacy of VNS is remarkably consistent among series, with an average decrease in seizure frequency of 40%, a 50% responder rate (i.e. the proportion of patients whose seizure frequency declined by at least 50%) usually ranging between 40 and 50% and a proportion of seizure-free patients below 5%. These figures appear stable over time, with no obvious indication of tolerance, although only a few long-term studies, with a follow-up period of more than three years, have been carried out in adults[8–13] or in children.[14–16] One puzzling limitation to the optimal use of VNS is the lack of a factor that reliably predicts its effectiveness.[17,18]

Whatever the type of epilepsy being considered, VNS is offered only to patients who continue to suffer from refractory seizures despite well-conducted medical treatments. The number of antiepileptic drugs (AEDs) that must be tested before concluding that the epilepsy is drug-resistant remains debatable, but a minimum of two is required. In practice, the majority of patients treated with VNS have previously received numerous AEDs as both monotherapy and polytherapy. Often, these patients have exhausted all other therapeutic options, including surgery, before VNS is proposed. In terms of the advantages and disadvantages of the various antiepileptic treatments, this strategy is not necessarily the most appropriate.

In this article, we aim to pragmatically address the current indications for VNS against the range of therapeutic, medical and surgical alternatives available for the treatment of refractory epilepsies.

Indications for Vagus Nerve Stimulation in Drug-resistant Partial Epilepsy

Vagus Nerve Stimulation versus Antiepileptic Drugs

No controlled study has directly compared the impact of adjunctive VNS versus AEDs alone in patients with drug-resistant partial epilepsy. Indirect comparison of the 50% responder and seizure-freedom rates observed during placebo-controlled trials suggests that the average efficacy of new-generation AEDs is comparable to that of VNS.[19] However, numerous factors complicate the interpretation of such indirect comparisons, including significant differences in terms of tolerability profile, ease of use, interruption of treatment and delay of efficacy. Globally, VNS offers the advantage of more favourable central nervous system tolerability than AEDs, but at the price of possible aesthetic concerns or intermittent vocal disturbances, with a delay in efficacy that can often be deferred for several months.

It is for this reason that a direct and global comparison of the effects of VNS and AEDs, incorporating quality of life measurements, is needed to assess the respective benefits of these two therapeutic approaches. This is currently being undertaken as part of an international randomised controlled trial, the PuLse study. The rationale for this study rests on the one hand on the observation that, following the failure of three successive AEDs, the addition of a new drug has very little chance of achieving a seizure-free outcome while often being responsible for disturbing side effects,[20] and on the other hand on the notion that VNS might allow a reduction in the number of concomitant AEDs and related side effects.[9,21–23] However, recent studies suggest that only a minority of VNS-treated patients experience a significant reduction in their AED load.[11,13,24] It is therefore too early to answer the question of whether VNS should be proposed after the failure of only a few AEDs, or instead after all available drugs have been tested.

Vagus Nerve Stimulation versus Resective Surgery

Traditionally, it has been assumed that VNS should be proposed only for those patients who have been rejected for epilepsy surgery.[8,11–13,25–28] However, this issue may deserve to be challenged and discussed on a case-by-case basis in the two following situations: first, patients who fulfil the criteria of a good surgical candidate but emphatically refuse brain surgery, generally because of an excessive fear of potential complications; and second, patients with very severe epilepsy in whom surgery can be contemplated despite a high risk of failure and/or functional post-operative deficit. Under such conditions, it would appear legitimate to

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consider VNS as a sound alternative treatment, in as much as this would not rule out later surgery. Another potential indication for VNS is represented by the failure of resective surgery. A few studies suggest that these patients are less likely to respond to VNS than the general population of patients with drug-resistant partial epilepsy,[29,30] but this issue remains controversial.[8,17,31,32]

Profiling Vagus Nerve Stimulation Responders

As a Function of the Side and Localisation of the Epileptogenic Zone

A few studies have evaluated whether the lateralisation of the epileptogenic zone (EZ) influences the efficacy of VNS, and showed only a non-significant trend towards a slightly higher rate of responders among patients with a right-sided EZ.[8,12] Other small series have reported non-significant trends towards greater efficacy in patients suffering from temporal unilateral,[25,33] bitemporal[34,35] or frontal lobe epilepsy.[8,32] Thus, at present there is no strong indication that the antiepileptic effect of VNS depends on the side or localisation of the underlying EZ.

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As a Function of the Underlying Lesion

Some studies suggest that VNS is more effective in patients whose epilepsy is symptomatic of an underlying brain lesion, most notably malformation of cortical development,[12,26] including tuberous sclerosis.[36,37] However, this issue remains controversial, with other series showing greater efficacy of VNS in patients with non-lesional epilepsies,[38] or comparable findings in patients with and without abnormal findings on magnetic resonance imaging (MRI).[17,33]

As a Function of the Associated Co-morbidity

A significant number of patients with refractory epilepsy also suffer from depressive co-morbidity, at times promoted by AEDs. In contrast, VNS has been shown to have antidepressive properties in patients with epilepsy, regardless of its impact on seizure frequency.[39] This finding led to the development of several VNS studies in non-epileptic patients with drug-resistant major depressive disorder, confirming the positive impact of VNS on mood disorders.[40–46] In the same way, VNS allows for improvement in the quality of life and behaviour of epileptic patients, including those who do not benefit from a significant reduction in seizure frequency.[47–51] All of these findings suggest that VNS might be particularly useful in the management of patients with both refractory seizures and depressive co-morbidity.

As a Function of Age

In three large paediatric trials, the 50% responder rate was found to be equal to or greater than that reported in adults, ranging from 46 to 83% after two years of follow-up.[14,15,52] Tolerability also proved comparable to that observed in adult populations.[14,15,52]

Indications for Vagus Nerve Stimulation in Refractory Generalised Epilepsy

Several studies suggest that VNS is effective in drug-resistant idiopathic or symptomatic generalised epilepsy.[8,12,23,24,53–55] The average reduction in seizure frequency appears comparable in these types of epilepsies (around 45% for follow-up ranging from three to 21 months) to that observed in partial epilepsies,[7,54,55] although a few studies suggest that higher responder rates could be observed in patients with symptomatic generalised epilepsy, specifically.[8,12,24] VNS appears to be efficacious against all types of generalised seizures, including myoclonic jerks,[23,55] tonic seizures,[54] absences and generalised tonic-clonic seizures.[8,23] In Lennox-Gastaut syndrome, the average reduction in seizure frequency was found to be greater for atypical absences and tonic seizures (73 and 55%, respectively) than for partial seizures (23%).[56] However, the efficacy of VNS in Lennox-Gastaut syndrome remains a controversial issue.[14,15,57–59] In childhood absence epilepsy, where about 5% of patients are drug-resistant,[60] VNS was evaluated in a multicentric study of 16 children with a mean age of eight years.[61] The 50% responder rate was 38% after six months of follow-up, rising to 88% at 18 months. Conversely, in infantile spasms VNS does not seem efficacious, with only two responders out of a series of 10 patients.[62]

Vagus Nerve Stimulation versus Callosotomy

The anecdotal observation that VNS might be particularly efficacious against seizures associated with traumatic falls has led to the comparison of VNS with callosotomy in adult patients suffering from generalised seizures.[63] The 50% responder rate for tonic and atonic seizures was comparable between the VNS and callosotomy groups (67 and 78%, respectively), while there was a non-significant trend towards a higher rate of complications in the group treated with callosotomy (21%, including 3.8% of permanent deficits) than in the VNS group (8%, with no permanent deficit). Comparable findings were recently reported in a series of 24 children suffering from Lennox-Gastaut syndrome.[64] VNS might thus be considered an appropriate alternative to callosotomy in patients suffering from generalised seizures associated with traumatic falls.

Past or Future – Vagus Nerve Stimulation versus Deep Brain Stimulation

Several methods of deep brain stimulation (DBS) have been developed over the past 30 years using multiple brain targets such as the anterior and central median nuclei of the thalamus, the subthalamic nucleus, the caudate nucleus or even the cerebellum. The majority of studies have been carried out on small groups and have not been properly controlled, and the results are highly variable and often contradictory. For instance, the encouraging results observed with stimulation of the central median nucleus of the thalamus were not confirmed by a double-blind, randomised study.[65–68] Similarly, six series on a total of 27 patients have evaluated the stimulation of the anterior nucleus of the thalamus in patients suffering from drug-resistant focal or generalised epilepsies, showing an average reduction in seizure frequency varying from 14 to 76%.[69–74] A large double-blind, randomised study is currently under way, and is hoping to reach a conclusion on the true effectiveness of this type of stimulation.[75] In any case, the potential indications of DBS in epilepsy appear similar to those of VNS. Assuming that the trials that are under way confirm the antiepileptic action of some forms of DBS, it would become essential to directly compare these techniques with VNS with a view to evaluating their respective risks and benefits.

Risks, Side Effects and Contraindications for Vagus Nerve Stimulation

Immediate Operative and Post-operative Complications

A peri-operative complication of VNS is the occurrence of cardiac dysrhythmias. According to the manufacturer's database, in 98 out of 60,014 implantation procedures the patient developed asystole or bradycardia during implantation of the VNS.[76] Detailed reports were available in seven patients,[77–79] showing that asystole resulted from a complete auriculo-ventricular block, while atrial rhythm was normal.[79] This is consistent with the functional anatomy and physiology of the left vagus nerve, which primarily supplies the atrio-ventricular node and has a negative chronotropic effect (while the right vagus nerve innervates the sino-atrial node). Nevertheless, the cause of this complication remains uncertain. In order to minimise the impact of this rare side effect, a systematic verification procedure in the operating room has been proposed:

- check the placement of the stimulation electrode in contact with the left vagus nerve;
- locate the branches that supply the heart in order to avoid the simultaneous stimulation of these branches and the vagus nerve;
- check the polarity of the lead and stimulator;
- ensure the absence of pooled blood or saline solution near the stimulation electrode after nerve irrigation; and
- conduct the system diagnostics in the operating theatre according to the specific pulse generator model.

A recent follow-up study of three patients who suffered bradycardia in the operating room and who were subsequently treated with VNS showed that no further abnormality of cardiac rhythm occurred during chronic stimulation.[80] Thus, the occurrence of bradycardia in the operating room does not represent a definitive contraindication to starting VNS, but requires close monitoring at the time stimulation is initiated. Furthermore, recent results confirm the lack of significant changes in cardiac rhythm and blood pressure between the on and off stimulation phases in patients treated with VNS for long periods.[81] On the other hand, the occurrence of unusual discomfort and, especially, unexpected falls in a patient who has been stabilised by VNS is an indication for an electrocardiogram to look for a cardiac dysrythmia.[82] Another uncommon post-operative complication is infection of the implantation site.

Sleep Apnoea Syndrome

A polysomnographic study was carried out on 16 patients before and three months after implantation of the VNS. Two patients presented with pre-operative pathological sleep apnoea and five presented after three months of treatment.[83] The sleep apnoea index had further increased in 14 of the 16 patients, although this did not reach the pathological threshold in the majority of cases. Breathing difficulties were significantly more frequent during the on phase of VNS than during the off phase, suggesting the direct role of vagus stimulation on respiratory function. A case report suggested that this phenomenon is dependent on the intensity of the stimulation.[84] The worsening of sleep apnoea syndrome (SAS) is also liable to encourage the occurrence of seizures, particularly nocturnal ones. It is therefore recommended to check SAS in all patients being proposed for VNS and, if in doubt, to perform a polysomnographic study. If the latter confirms the diagnosis of SAS, the SAS should be treated first since it might have a favourable effect on seizures. If the epilepsy remains drug-resistant despite SAS treatment, it might still be appropriate to consider the indications for VNS in this context, but this would require closely monitoring the evolution of SAS.

Other Common Side Effects

Insertion of the VNS can cause aesthetic concerns due to the extent of the scar, notably on the neck, and of a stimulator-related skin bulge, particularly in slim people. Good surgical technique and the smaller stimulators that have recently been developed can minimise these problems. Stimulation, typically carried out using 30-second cycles every five minutes, is often associated with a hoarse voice, which decreases over time and rarely represents a significant concern for the patient. On the other hand, the impact of VNS on the upper airways can reduce respiratory capacity in patients actively engaged in sports activities, notably running. More rarely, VNS may be responsible for variable pain at the point of stimulation in the neck, requiring a reduction in stimulation by adjusting the VNS parameters.

Other Drawbacks of Vagus Nerve Stimulation

Patients receiving VNS must be informed of the delayed antiepileptic efficacy of the procedure (typically progressing over several months), the difficulty of removing the vagal electrode and the need to replace the battery after an average period of five years.

Conclusion

VNS is an effective, though usually not curative, antiepileptic treatment aimed at patients with drug-resistant epilepsy, either partial or generalised, for which no simple medical or surgical cure can be proposed (failure of more than three AEDs, patient not eligible for surgery, patient reluctant to be operated on or patient at high risk of surgical failure or complications). VNS is of particular benefit due to its unique tolerability profile, with some advantages over AEDs (no organ toxicity, drug interaction, immunoallergenic side effects or toxicity of the central nervous system that compromise sight, cognitive functions, mood or behaviour), but also disadvantages linked to its aesthetic, vocal and respiratory consequences. Numerous unanswered questions remain relating to the mechanisms of action, identification of future responders and value of VNS above and beyond its current use as a treatment of last resort, notably in combination with new AEDs. ■

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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.

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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.

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[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.

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