Setting Up a Successful Vagus Nerve Stimulation Service for Patients With Difficult-to-Treat Depression

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ABSTRACT

Background: A substantial number of patients with major depressive disorder (MDD) do not sufficiently remit after the first lines of antidepressant treatments, making them vulnerable to poor clinical outcomes. Patients who have not had adequate resolution of their depressive symptoms after four antidepressant treatments and/or have been experiencing their current episode of MDD for two years or more (with insufficient responses to adequate antidepressant treatments) should be evaluated for antidepressant vagus nerve stimulation (VNS Therapy). Adjunctive VNS Therapy is a promising long-term treatment option for patients with difficult-to-treat depression (DTD), offering significantly improved remission rates in comparison with usual treatments. However, VNS Therapy requires specialized treatment centers to support patients.

Materials and Methods: In this narrative review, we aim to outline the necessary steps for setting up an antidepressant VNS Therapy service in an efficient manner.

Results: Establishing a VNS Therapy service requires several high-level considerations: initiation of a collaborative multidisciplinary team of health care professionals; developing a surgical pathway for implantation; consideration of reimbursement and health care coverage; setting up a specialist clinic to identify optimal candidates for VNS Therapy; educating patients and their families about VNS Therapy; and training health care providers on patient-specific VNS Therapy treatment and long-term treatment management.

Conclusions: Antidepressant VNS Therapy is a promising treatment option for the long-term treatment of patients with DTD. We have successfully initiated four VNS Therapy service centers for DTD in the United States, Austria, and Germany. Based on our experiences and lessons learned, herein, we have provided advice to psychiatric centers planning to set up a VNS Therapy service for their patients with DTD.

Keywords: Depression, difficult-to-treat depression, treatment-resistant depression, vagus nerve stimulation, VNS

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BACKGROUND

Depression is a leading cause of disability worldwide.¹ Most patients with depression successfully remit after initial attempts with standard antidepressant treatment options. Unfortunately, approximately one-third of patients experiencing a major depressive episode have insufficient responses to multiple adequate antidepressant therapies and are considered to have treatment-resistant depression (TRD).^{2–6}

The term “difficult-to-treat depression” (DTD) is recently gaining preference over the term “treatment-resistant depression” because it is considered to be an inclusive, less stigmatizing term that recognizes the complexities of creating an effective and long-term treatment plan and may encourage patients and clinicians to consider a broader range of treatment options that work synergistically to achieve short- and long-term treatment goals.^{5–7}

Difficult-to-Treat Depression

Patients with DTD have significantly higher medical and psychiatric health care costs and more medical utilization for nonpsychiatric conditions than patients with depression who successfully respond to standard treatment options.^{8–11} DTD is associated with increased morbidity and mortality, and patients with DTD experience substantial decrements in their quality of life owing to the adverse impacts on their role and function in society.^{3,12} In addition, frequent^{8–11} major depressive episodes of long duration are accompanied by substantial structural and functional changes in the brain.¹³ Therefore, it is imperative to identify an adequate treatment regimen to manage this neuroprogressive illness.

For patients who do not successfully remit after first-line antidepressant therapies (including psychotherapy and pharmacotherapy with selective serotonin reuptake inhibitors or similar substances), some of the current clinical recommendations include augmentation strategies, switching classes of antidepressants, and electroconvulsive therapy (ECT).^{14,15} However, some antidepressant treatments, including ECT, have substantial relapse rates following acute response, remission, and recovery, and these subsequent depressive episodes are often of longer duration, more severe, and less responsive to treatment.^{16,17}

To overcome obstacles of nonresponse to adequate treatments, novel antidepressant treatment options should be considered, such as ketamine and vagus nerve stimulation (VNS Therapy® System; LivaNova USA, Inc, Houston, TX).^{18–22}

Adjunctive VNS Therapy as a Treatment Option for DTD

VNS Therapy is an approved adjunctive treatment option for patients with DTD and has been implanted in more than 4000 patients with DTD over the past 20 years (data on file; LivaNova PLC).^{21,22}

The VNS Therapy System includes a small pacemaker-like pulse generator, a thin, flexible silicone lead, a nerve stimulation electrode, and an external programming system that is used to change the stimulation settings (Fig. 1).^{21,22} Using a minimally invasive reversible surgical procedure, the generator and the thin, flexible silicone lead or electrode are surgically implanted subcutaneously in the pectoral region (usually the left side) and in the neck, respectively. The generator is housed in a hermetically sealed titanium case and is powered by a single battery. The external programming system allows the stimulation settings to be adjusted by the treating clinician to deliver patient-specific mild intermittent electrical stimulation to the patient's left vagus nerve at regular intervals around the clock, 24 hours a day, every day. The stimulation elicits action potentials in the vagal fibers that synapse in the brainstem.

In patients with high burdens of major depressive disorder (MDD), the available clinical evidence indicates a beneficial effect of adjunctive VNS Therapy with treatment-as-usual (TAU) in both response and long-term remission rates as well as an improvement in quality-of-life measures over time compared with TAU alone.^{23–37}

The largest data set supporting the use of adjunctive VNS Therapy in the treatment of DTD demonstrated favorable outcomes in 494 participants who received adjunctive VNS Therapy plus TAU vs 301 patients with DTD who received only TAU.²⁵ The VNS + TAU group had a significantly higher five-year cumulative response rate (67.6% compared with 40.9%) and a significantly

Figure 1. The VNS Therapy System includes a pulse generator, a silicone lead, a nerve stimulation electrode, and an external programming system that is used to change the stimulation parameters. [Color figure can be viewed at www.neuromodulationjournal.org]

higher remission rate (cumulative first-time remitters, 43.3% compared with 25.7%). Notably, patients with bipolar DTD were found to be just as likely to respond to treatment with VNS Therapy as those with unipolar DTD.²⁵ An exploratory analysis of this study showed that adjunctive VNS Therapy is associated with a shortened latency to first response and a higher probability of maintaining response, implicating VNS Therapy as an effective adjunctive tool for relapse prevention in the long-term management of DTD.²⁶

Treatment with adjunctive VNS Therapy with TAU has been shown to be more effective than TAU alone in reducing depressive symptoms and suicidal ideation in patients with depressive episodes of very long durations, a high number of previous ECT treatments, and suicidal attempts.^{25,38,39} In addition, treatment with VNS Therapy has a low risk of inducing switches of depression to hypomanic/manic symptoms or inducing suicidality.²⁴

A comprehensive systematic literature review by Bottomley et al⁴⁰ included 22 clinical efficacy and safety studies to assess the outcomes of longer-term treatment with adjunctive VNS Therapy. Based on their review, the authors concluded that the antidepressant benefits of adjunctive VNS Therapy improved over 24 months with minimal safety concerns, and the authors additionally reported either a maintenance or a modest improvement in the patients' quality of life with adjunctive VNS Therapy.

Another systematic review described the long-term effectiveness of VNS Therapy in patients with DTD based on five studies with Level II evidence (methodologically well-defined, controlled non-randomized study or methodologically adequate, quasi-experimental study) and four studies with Level III evidence (methodologically adequate, nonexperimental descriptive study) (Table S1).^{41,42} In these studies, approximately one-third of patients experienced a 50% reduction of depressive symptoms in the first year of therapy, and two-thirds of these patients maintained the response at long-term follow-up.^{25,28,29,38,43–47}

As presented in Table S1, additional publications of studies evaluating adjunctive VNS Therapy have been published in the past few years^{26,27,39,48–52} that further support the findings from the reviews by Bottomley et al⁴⁰ and Dibué-Adjei et al.⁴¹

Despite the limitations in the available clinical evidence, the published findings support the notion that adjunctive VNS Therapy is associated with higher response, remission, and quality-of-life outcomes compared with TAU, and the maximal treatment effects are often observed after 12 months (or longer) of stimulation.

Positioning VNS Therapy in the Antidepressant Treatment Regimen

An important consideration for psychiatrists is how to position VNS Therapy in relation to other available antidepressant treatment modalities. The current treatment guidelines offer variable suggestions for when novel antidepressants (such as VNS Therapy) should be considered.²⁰ For example, 1) the current guidelines from the American Psychiatric Association on management of MDD emphasize the role of VNS Therapy as a treatment option in the long-term treatment of patients who have not responded to at least four adequate trials of depression treatments, including ECT¹⁴; 2) the guidelines from the British Association for Psychopharmacology state that VNS Therapy could be considered in patients with chronic and/or recurrent depression who have failed to respond to four or more antidepressant treatments⁵³; and 3) the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines recommend VNS as a third-line neuromodulatory treatment after

repetitive transcranial magnetic stimulation (rTMS; first line) and ECT (second line).⁵⁴

An optimization scheme for sequential antidepressant treatments was recently proposed for acute and chronically ill patients with MDD to support early recognition and early adequate treatment to optimize treatment outcomes.²⁰ The treatment scheme suggests sequential consideration of antidepressant treatments as stage 1 (monotherapy/dose escalation) and stage 2 (augmentation/switch) within three months of the first episode of MDD. Patients classified as having DTD but whose antidepressant treatments were not confounded by “pseudo resistance” factors are to be considered for stage 3 (novel antidepressant treatments) and stage 4 (repetition of previous stages or experimental treatments). According to the proposed sequential treatment optimization scheme, VNS Therapy is a stage 3 therapy for patients with DTD.²⁰

The landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial sponsored by the National Institute of Mental Health included more than 4000 adult patients with nonpsychotic MDD who were candidates for antidepressant drugs as a first-line treatment step.⁴ Patients who did not achieve remission or could not tolerate a treatment step proceeded to the next acute treatment step. The other patients who achieved remission and tolerated acute treatment or experienced meaningful improvement and acceptable tolerability entered a longer-term naturalistic follow-up phase. The STAR*D trial results showed that about 30% of adult patients with nonpsychotic MDD fail to remit after four trials of antidepressants, resulting in a large population of individuals who are symptomatically and functionally impaired.⁴ Based on the evidence from the STAR*D trial, the current treatment guidelines, the antidepressant treatment optimization scheme, and our own experience, we propose that patients who have not had adequate resolution of their depressive symptoms after four antidepressant treatments and/or have been experiencing their current episode of MDD for two years or more (with insufficient responses to adequate antidepressant treatments) should be evaluated for treatment with VNS Therapy.^{4,14,20,24,53,54}

VNS THERAPY SERVICE CENTER FOR THE TREATMENT OF DTD

VNS Therapy requires specialized treatment centers to support patients. Setting up such a service center can take several months. We (the authors) have successfully initiated VNS Therapy service centers for DTD in specialized hospitals providing secondary or tertiary care in United States, Austria, and Germany. Based on our experiences and lessons learned, herein, we present information on several high-level topics for consideration when setting up a VNS Therapy service center (Fig. 2), including setting up a collaborative multidisciplinary team of health care professionals; developing a surgical pathway for implantation; considering reimbursement and health care coverage; setting up a specialist clinic to identify optimal candidates for VNS Therapy; educating patients and their families about VNS Therapy; and training health care providers on patient-specific VNS Therapy treatment and long-term treatment management.

Setting Up a Multidisciplinary Team of Health Care Professionals

The necessity of VNS Therapy and the indication should be determined by the treating psychiatrist or primary care physician,

Figure 2. Establishing a VNS Therapy service center for patients with DTD requires several high-level considerations. [Color figure can be viewed at www.neuromodulationjournal.org]

who will have primary responsibility for dose titration and long-term management of the patients and the implanted devices. Nonetheless, a VNS Therapy service requires a multidisciplinary team of health care professionals (including psychiatrists, psychologists, psychotherapists, nurses, and social workers) who can efficiently collaborate with each other and provide long-term support to patients, from selection of VNS Therapy to follow-up care after VNS device implantation. The service personnel with the appropriate skills and competencies should receive additional training from the device manufacturer about prescription, implantation, postoperative care, and device titration procedures.

In our experience, clinical VNS treatments are currently conducted within specialties, ie, pediatricians or neurologists treat patients with epilepsy, and psychiatrists treat patients with depression. If feasible, leveraging opportunities to work with and secure learnings from established VNS centers treating patients with epilepsy should be explored. Such an interdisciplinary collaboration may expedite setting up a VNS clinic for DTD by facilitating knowledge transfer on surgical procedures, postoperative care, and side effect management, as well as treatment of patients who meet both diagnoses of epilepsy and depression.

Developing a Surgical Pathway for Device Implantation Surgery

Implanting a VNS Therapy device consists of three key steps: placement of the electrode contacts around the vagus nerve, tunneling of the electrode leads to the left chest wall, and placement of the pulse generator into a subcutaneous pocket (Fig. 1). The implantation surgery is typically performed under general anesthesia during an inpatient or outpatient visit and involves a standard minimally invasive and reversible surgical procedure that takes one to two hours. After connecting the implantable pulse generator to the electrodes, the surgeon tests the device to ensure its functionality before closing the incisions. Device stimulation is activated approximately two weeks after implantation.

When developing a surgical pathway, it is important to establish a relationship with a surgeon in advance and consider the availability of the primary surgeon as well as the availability of alternative surgeons during occasions when the primary surgeon is unavailable. It is also important to consider how often the primary and alternative surgeons perform urgent and emergency procedures that may delay VNS Therapy placement because it is considered an elective procedure. Communicating directly with the surgeon's office staff may assist with coordinating pre- and postoperative care as well as other important logistics (eg, billing, preoperative examination clearance, and postoperative follow-up appointments).

Before VNS Therapy placement, patients who are candidates for surgery must complete a preoperative physical examination and necessary testing to identify and optimize conditions that decrease perioperative morbidity and mortality. Patients with certain comorbidities, other implanted devices, or previous surgeries may require specific preoperative investigations to evaluate the general perioperative risk.

Many neurosurgeons have training and experience with VNS Therapy device implantation. In addition, implantation can also be performed by otolaryngologists, vascular surgeons, and general surgeons who are trained in surgery of the carotid sheath and have received specific training in the implantation of the device.^{21,22} We have found that support from the latter specialties provides a successful pathway in overcoming the long waiting periods in neurosurgical departments.

Consideration of Reimbursement and Health Care Coverage

Reimbursement for the costs associated with VNS Therapy varies by country and may vary by hospital. Clinicians should explore the coverage options before evaluating patients for VNS Therapy.

In 2001, VNS Therapy received the CE Mark in Europe for the treatment of chronic or recurrent depression in patients who are in a treatment-resistant or treatment-intolerant major depressive episode.²² In some European countries, including Germany and Austria, a comprehensive health care system ensures that the costs of implantation and long-term management of VNS Therapy for DTD are covered by a patient's health insurance. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) guidance states that clinicians may use the procedure in patients with DTD with special arrangements for clinical governance.¹⁵

In 2001, Health Canada approved VNS Therapy for the treatment of chronic or recurrent depression in patients who are in a treatment-resistant or treatment-intolerant major depressive episode.⁵⁵ Currently, billing codes are established in Canada for implantation, and there is reimbursement for the cost of the VNS system in some regions of Canada.

In the United States, beneficiaries of the national Medicare insurance program are currently not covered to receive VNS Therapy for DTD. Coverage is usually based on a patient's unique clinical circumstance, and case-by-case approvals have been obtained from different insurance payers. Several appeals steps may be required to gain coverage, and the process and number of steps vary by US state and by health insurance plan. Insurance companies may also require previous authorization for generator replacement procedure following battery depletion, which may cause clinically significant delays because prompt replacement of

the generator before end of service is appropriate to decrease the risk of possible relapse. In the United States, knowledgeable service personnel may be able to help determine if specific insurance plans will cover aspects of the VNS Therapy procedure by verifying a patient's benefits and determining the best way to pursue approval.

Identification of Optimal Candidates for VNS Therapy

Treatment of patients with DTD poses a challenge to psychiatrists and primary care physicians because there are no available reliable prognostic markers on response and remission to indicate which patients will benefit from first-line therapies.²⁰ As such, DTD remains underdiagnosed and undertreated.

Diagnosis of DTD

DTD is a complex clinical phenomenon that is influenced by heterogeneity with varying degrees of severity in depressive subtypes, psychiatric comorbidities, and coexisting medical illnesses. Given the syndromic nature of depression diagnostics based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* and the *International Classification of Diseases (ICD)*, it would not be uncommon for an individual to exhibit symptomatology consistent with DTD when the etiology of their depressive symptoms is attributable to another psychopathology. Thus, important considerations for identification of DTD include an evaluation of underlying substance use disorders, severe personality pathology, and major neurocognitive disorders.

Preliminary Criteria for Identifying Candidates for VNS Therapy

The guidelines on consideration of VNS Therapy for DTD sometimes vary by country. Each center should develop center-specific

patient screening criteria and selection checklists in adherence with applicable national and international clinical guidelines. Such an infrastructure will assist in identifying patients who are optimal candidates for VNS Therapy and may potentially benefit from the treatment.

According to a recently published roadmap from the Newcastle Regional Affective Disorders Service, VNS Therapy should be reserved for patients with the capacity to provide informed consent and may not be suitable for patients with a high surgical risk, sleep apnea, a significant personality disorder overshadowing the mood disorder, or a significant active substance misuse disorder.⁵⁶ The authors suggest that VNS Therapy should be considered for patients with a primary diagnosis of MDD or bipolar disorder (currently depressed or predominantly depressive polarity); with the current depressive episode of more than two years in duration or the patient has had three previous episodes; and who meet one or more of the following criteria:

- Patient responds to ECT but is unable to sustain the response and experiences a relapse, thus requiring repeat courses (eg, ≥ 2 ECT courses in the past two years) or maintenance ECT.
- Patient failed to respond, achieve remission, maintain a response/remission, or tolerate ≥ 2 trials of structured psychologic therapy, ≥ 4 antidepressants, ≥ 2 augmentation strategies, and ECT.
- Patient has a history of high health care service utilization, clearly indexed by multiple hospital admissions for their depression and/or a hospital admission for depression that was more than six months in duration.

Similar to the structured list published by the Newcastle Regional Affective Disorders Service to evaluate patient eligibility, we have

Figure 3. Preliminary screening of patients with DTD for adjunctive VNS Therapy based on the approved label in the United States. DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. [Color figure can be viewed at www.neuromodulationjournal.org]

prepared Figure 3 to guide identification of candidates who may be eligible for VNS Therapy based on the approved label in the United States.^{14,21,57} Additional considerations when evaluating patients for VNS Therapy (such as patients who may benefit from VNS Therapy, contraindications, and comorbidities leading to ineligibility) are provided in Figure 4. Importantly, a patient should not be “prophylactically” treated with VNS Therapy while euthymic, even if the patient has a history of frequent recurring depression.

Patient Education

It is important for patients, their caregivers, and families to learn about treatment options for DTD, as well as the efficacy and safety profile of VNS Therapy, the implantation procedure, potential side effects associated with implantation and stimulation, pre- and postoperative care, the need for regular follow-up visits with the treating physician to adjust the stimulation parameters, and long-term care.

The service centers should provide information to patients to support them in making informed decisions about treatment with adjunctive VNS Therapy (Table S2 for an example of a patient information sheet). Treating physicians should encourage patients to ask questions and provide patients with accurate and comprehensive responses.

An important consideration to communicate with patients is that VNS Therapy is a slow-acting antidepressant treatment and requires long-term stable follow-up periods; therefore, managing patient expectations is very important. If possible, patients and their support team should have the opportunity to hear from other patients about their experience with VNS Therapy.

Patients should be instructed on the following two important factors: 1) patients should inform other treatment providers about their VNS Therapy implant, because surgical or diagnostic procedures may need to be adapted with an implanted VNS Therapy; and 2) in the event of uncomfortable adverse events, continuous stimulation, or other malfunction, patients should hold or tape the

magnet directly over the implanted generator to prevent additional stimulation (ie, output current will be 0 mA). If patients or caregivers find this procedure necessary, they should immediately notify the patient's physician.

Physicians should always try reducing the output current as a means of eliminating or reducing the severity of an adverse event.

Postoperative Care and Programming of VNS Therapy Dosing Parameters

Postoperative Care

VNS Therapy System is an adjunctive therapy to existing antidepressant medications. Per the prescribing label, physicians are strongly encouraged to keep all antidepressant medications stable for the first three months of stimulation before attempting to reduce or change a patient's medication.^{21,22} The patient should be seen during the first few weeks after implantation by the surgeon to confirm wound healing and proper generator operation.

Personnel Training

VNS Therapy should be prescribed, monitored, and programmed by physicians who have specific training and expertise in the management of DTD and the device use. Antidepressant VNS Therapy treatment does not require specialized technical skills because stimulation parameters are adjustable by remote programming devices with intuitive user interfaces but requires proper training before device use and support. At least two to three service center personnel should receive proper training from the device manufacturer on programming the VNS Therapy device. The primary trained clinician can be a psychiatrist. Additional trained staff can include psychiatrists, psychologists, nurses, and other allied health professionals.

All programming should be conducted by or under the supervision of a physician familiar with the use and operation of the programming software.^{21,22}

1. Additional patients with DTD who may benefit from adjunctive VNS Therapy:

- Unable to maintain remission or response
- Residual symptoms on ECT or ketamine maintenance treatment needing adjunctive treatment or to reduce the frequency of ECT or ketamine maintenance treatment
- Receiving treatment with high doses of antidepressant medications and/or experiencing a high load of adverse events needing adjunctive treatment

2. Contraindications:

- VNS Therapy cannot be used in patients after a bilateral or left cervical vagotomy
- Shortwave diathermy, microwave diathermy, or therapeutic ultrasound diathermy cannot be used on patients implanted with VNS Therapy

3. Comorbidities that may lead to ineligibility for VNS Therapy:

- Presence of any other leading primary psychiatric diagnosis (other than unipolar or bipolar major depressive disorder)
- Presence of cardiac arrhythmias or progressive neurological disorder including high likelihood for a neurosurgical intervention
- Experiences depressive episode with predominant psychotic features or predominant personality disorder
- Substance use disorder
- Neurodegenerative disorder, cognitive impairment, or mental retardation

Figure 4. Additional considerations when evaluating patients with DTD for adjunctive VNS Therapy. [Color figure can be viewed at www.neuromodulationjournal.org]

Figure 5. VNS Therapy stimulation parameters should be steadily optimized relying on attentive patient-specific titration. [Color figure can be viewed at www.neuromodulationjournal.org]

Titration of Stimulation Parameters

The VNS Therapy System is programmed by clinicians using an external programming device and relying on attentive patient-specific titration to select the right combination of adjustable parameters (output current [mA], signal frequency [Hz], pulse width [µs], and signal ON and OFF times) to attain full activation of the vagus nerve while minimizing stimulation-induced side effects.

Dose titration may occur in either inpatient or outpatient settings. During initial programming, the output current should be programmed to start at nominal parameters (0 mA) and then be gradually increased in 0.25-mA increments until the patient feels the stimulation at a comfortable level (Fig. 5). Patients who are receiving replacement generators should also be started at nominal parameters, with increases in 0.25-mA increments to allow re-accommodation. A standard starting dose would have an output current of 0.25 mA to 0.50 mA, with a frequency of 20 Hz, and a pulse width of 250 µs with 30 seconds ON and 5 minutes OFF.

Patients will need frequent dosing visits during the first months of VNS Therapy to reach a maximum tolerated dose in the shortest possible period. Most clinicians follow a steady titration schedule, starting approximately two weeks postimplant, in which the output current is steadily increased weekly over the subsequent four weeks. For individual patients, the dose titration period can be extended if needed. However, if a patient continues to experience intolerable side effects related to stimulation after six weeks of dose titration, the highest tolerable dose for that patient should be evaluated and continued.

It is important for service center personnel to learn to titrate patient-specific stimulation parameters safely and quickly to reach a therapeutic dose range because this is crucial to ensure the highest probability for an early response.⁵⁸

Currently, there is no proven correlation between high output current and device effectiveness; however, available clinical data indicate that higher charges may be beneficial for maintenance of response and support the dose-response relationship between charge and likelihood of response. In a clinical study, higher electrical dose parameters were associated with response durability and correlated with a reduction of depressive symptoms.²⁹ The median therapeutic treatment settings were 1.25 mA (range: 0–2.5 mA), 20 Hz frequency (range: 1–30 Hz), 250 µs pulse width (range: 130–500 µs), 30 seconds ON time (range: 7–60 seconds), and 5 minutes OFF time (range: 0–180 minutes); however, there are no data to verify that these are optimal parameters.

Individual patient tolerability is a critical consideration during the dosing process because a higher output current may be associated with less tolerability, and time to adapt to an increased dose should be considered. Importantly, treatment with VNS Therapy should not be uncomfortable and should not cause intolerable side effects.

At each visit, patients should be observed for at least 30 minutes after the dose titration process to make certain that they are comfortable with the adjusted programmed stimulation. Transient effects such as voice alterations may occur during the titration process.

The effect of duty cycle of the device may also play an important role in the reduction of symptomatology for patients with TRD. The percentage of time the generator is stimulating is called a “duty cycle” and is a measure of ON time compared with OFF time. Table 1 lists the duty cycles (highlighted with an asterisk) that are not recommended because they represent combinations with an ON time greater than the OFF time.

Patients who react well to VNS Therapy and whose depression is well controlled at follow-up should not have their settings changed unless they experience uncomfortable side effects. The subsequent follow-up schedule and the nature of each examination should be determined by the physician based on patient response.

Titration visits usually last less than one hour. To support logistical challenges (eg, if a patient resides far away from the VNS service center), some centers have shortened the titration period and have titrated the devices in an inpatient setting over three to four days, during which doses are gradually increased until a therapeutic dose is reached.

Consideration of Safety Findings Related to Adjunctive VNS Therapy

Overall,^{25,38,39} VNS Therapy is generally well tolerated and has high adherence and continuation rates.²⁸ The number (and percentage) of patients reporting an adverse event during the first and

Table 1. A List of Duty Cycles for Typical ON Time and OFF Time Settings.

	OFF time (min)								
	0.2	0.3	0.5	0.8	1.1	1.8	3	5	10
ON time (s)	Duty cycles (% ON time)								
7	58	44	30	20	15	10	6	4	2
14	69*	56	41	29	23	15	9	6	3
21	76*	64*	49	36	29	19	12	8	4
30	81*	71*	57	44	35	25	16	10	5
60	89*	82*	71*	59*	51	38	27	18	10

Duty cycle is calculated as duty cycle (%) = (ON time + 2 seconds of ramp-up time + 2 seconds of ramp-down time)/(ON time + OFF time [seconds]) × 100.

*These duty cycles are not recommended because they represent parameter combinations with an ON time greater than the OFF time.

Figure 6. Adverse events reported in $\geq 10\%$ of patients following implantation with VNS Therapy during year 1 (orange bars; of 700 patients) and year 2 (gray bars; of 344 patients). Each patient is counted only once per adverse event within each year, even though some patients may have reported multiple occurrences of the same event. [Color figure can be viewed at www.neuromodulationjournal.org]

second years on VNS Therapy is provided in Figure 6.²⁸ The most common adverse events include voice alteration (typically transient and occurs during the stimulation ON period), dyspnea, pain, increased cough, and incision pain, with a trend toward diminishing adverse events over a longer treatment period with VNS Therapy.²⁸ Decreasing the output current or ON time may help with eliminating or reducing the severity of an event. A dose effect in relation to tolerability was noted in some patients at 8 to 16 weeks after implantation.^{28,29}

Patients should be educated about potential adverse events as early as appropriate, eg, during the initial eligibility screenings.

Long-Term Treatment Follow-Up of Patients With VNS Therapy

Long-term follow-up of patients based on contacts and symptom monitoring is critical because the time to reach maximum clinical improvements is expected over a period of three months to one year after a therapeutic stimulation dose is reached. Importantly, VNS Therapy is likely to remain a long-term adjunctive treatment to ongoing antidepressant therapy because it has a long-term modulatory effect. Hence, antidepressant maintenance treatment is recommended. For follow-up visits, reduction of augmentative medication with potential side effects (such as second-generation antipsychotics or lithium) may be possible options if response and remission are maintained.

Assessments of mood and social function should be completed at baseline, at three and six months following implantation, and at subsequent six-month intervals.⁵⁶ A list of validated tools that are

relevant to the treatment of depression and are designed to be completed by either clinicians or patients is provided in Tables S3 and S4, respectively.

To assess treatment outcome on response and remission, utilization of standardized depression rating scales at each visit is recommended. Clinical benefit can be assessed on the basis of a $>25\%$ decrease from the baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score. Treatment response can be assessed on the basis of a $\geq 50\%$ reduction from the baseline MADRS score or a $\geq 50\%$ reduction from the baseline Hamilton Rating Scale for Depression (HAM-D) score. For the categorical CGI-I scale, a value of 1 (for “very much improved”) or 2 (for “much improved”) can be used to monitor treatment response.

Remission can be monitored using continuous score scales based on achievement of a score of ≤ 9 on the MADRS, ≤ 14 on the Clinician Administered Version and/or the Self-Report Version of the Inventory of Depressive Symptomatology (IDS-C and IDS-SR, respectively), or ≤ 5 on the Quick Inventory of Depressive Symptoms Clinician Administered (QIDS-C).

It is important to continue regular suicide risk assessment, including suicidal attempts and suicidal ideation, using the assessment of suicidality (“Has the patient made a suicidal gesture or attempt since the last visit?”) and a score of ≥ 4 on MADRS Item 10 (“Suicidal thoughts are common or explicit plans for suicide”). If feasible, each patient should be assessed by the same rater to ensure consistency.

In addition, assessments of a patient’s quality of life and functioning (such as working memory, verbal memory, concentration,

Pros	Cons
Antidepressant efficacy in patients with difficult-to-treat depression	Long-term randomized controlled trials are still ongoing
Long-term maintenance treatment lacking adherence issues	Implantation demands invasive neurosurgery
Alternative mechanisms of action compared with pharmacotherapy or electroconvulsive therapy	Access to a multiprofessional team is necessary
Improvements in quality-of-life measures	The treatment costs are not covered by medical insurance programs in many countries

Figure 7. Several pros and cons of adding antidepressant VNS Therapy to an existing treatment portfolio. [Color figure can be viewed at www.neuromodulationjournal.org]

processing speed, and executive functions) and a patient's treatment goals are highly recommended. Clinicians can use tools such as the Quality-of-Life Enjoyment and Satisfaction Questionnaire, EuroQol-5 Dimension (EQ-5D) from the European Quality of Life Scale (EuroQoL), or the World Health Organization Quality of Life Instrument (WHOQOL) developed by the World Health Organization.

In some cases, family members and caregivers may notice an improvement in mood and daily function before it is realized by the patient. Therefore, scales such as the Patient Health Questionnaire 9 (PHQ-9) can be completed by both the patients and their caregivers to assess improvements from different perspectives.

In addition to clinical response assessment, each patient should undergo a routine check of the VNS Therapy generator, lead resistance, and battery status. Eventually, all VNS Therapy generators require surgical replacement because of battery depletion. The device programming software provides notification when the generator battery is nearing or has reached end of service. Prompt replacement of the generator before end of service is appropriate to decrease the risk of possible relapse.

Some patients prefer to present to a VNS Therapy service solely for VNS maintenance and otherwise work with a different psychiatrist for medication management. To ensure optimal care for the patient, we recommend good communication with the primary psychiatrist (eg, consult note or direct phone call) regarding VNS setting adjustments and other relevant details.

Adverse events should be managed carefully because their persistence may diminish antidepressant response. To this end, dose adjustment through down-titration of output currents or reducing ON times may be a viable strategy. In the case of severe adverse events, the decision to switch the stimulation OFF for a certain limited period (eg, two weeks) should be carefully weighed against existing therapeutic benefits.

CONCLUSIONS

To date, the use of VNS Therapy has been primarily limited to highly specialized tertiary treatment centers. We recently initiated VNS Therapy service centers for DTD at the Rush University Medical Center (Chicago, IL), Washington University (St. Louis, MO), the Medical

University of Vienna (Vienna, Austria), and the University of Münster (Münster, Germany). Here, we have shared our recent experiences and lessons learned in establishing successful VNS Therapy services.

Service centers within hospitals can serve as models to efficiently identify and serve a larger number of patients with DTD who may potentially benefit from VNS Therapy. The opportunity to work closely with an established epilepsy center that provides VNS Therapy services may substantially facilitate procedures related to surgery, device ramp-up and dosing, and long-term follow-up care. In addition, personal experience from the authors suggests that centers that offer ECT procedures are highly suited in expanding their services to offer VNS Therapy because both neuromodulatory modalities are indicated in DTD.

There are limitations to treatment with VNS Therapy because it requires stable, long-term care and support, ideally from a multiprofessional team, which makes it less attractive for private practice and small outpatient clinics. Although sham-controlled trials are ongoing to further evaluate VNS Therapy, the side effects of the treatment are frequent and may be optimized in the future with technologic improvements. Several pros and cons of including VNS Therapy in the existing portfolio of antidepressant treatment are highlighted in Figure 7.

Notably, VNS Therapy is being investigated in the largest randomized controlled trial of any neuromodulatory treatment in DTD to date in the RECOVER trial (a pRspective, multi-cEnter, randomized Controlled blinded trial DemOnstrating the safety and effectiveness of VNS Therapy System as adjunctivE therapy versus a no stimulation control in subjects with treatment-Resistant depression), which will include up to 500 patients with bipolar DTD and 500 patients with unipolar DTD.⁵⁹ An additional ongoing study, RESTORE-LIFE (a global pRspective, multi-cEnter, obServational post-markeT study tO assess shoRt-, mid-, and long-term Effectiveness and efficiency of VNS Therapy as adjunctive therapy in real-world patients with difficult-to-treat dEpression), has been designed as a prospective, observational, multicenter, global postmarket study intended to assess the short-, mid-, and long-term effectiveness and efficiency outcomes in a "real-world" setting among a minimum of 500 patients with DTD treated with adjunctive VNS who will be followed for 36 to 60 months.⁶⁰ Disease diagnosis in RESTORE-LIFE will be based on the Mini International Neuropsychiatric Interview, and the primary end

point of response rate will be based on a $\geq 50\%$ decrease in the MADRS total score from baseline to 12 months postimplant.

The study results from RECOVER and RESTORE-LIFE are expected to become available starting in 2022 and may provide important insights in the future use and application of VNS Therapy in DTD. Until the results become available, the information provided here can serve as state-of-the-art evidence on how to initiate VNS Therapy service centers.

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Authorship Statements

Based on their clinical experience and success in setting up a VNS Therapy Service, Christoph Kraus, Darin Quach, David M. Sholtes, Erhan Kavakbasi, John Zajecka, and Bernhard T. Baune discussed and conceptualized the need for this manuscript. Christoph Kraus, Bernhard T. Baune, Maxine Dibué, and Renske De Zwaef prepared the manuscript draft, with important intellectual input from Darin Quach, David M. Sholtes, Erhan Kavakbasi, and John Zajecka. All authors approved the final manuscript. All authors reviewed and approved the manuscript, tables, and figures. The authors made the decision to submit the manuscript for publication and vouch for the information included in this manuscript.

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SUPPLEMENTARY DATA

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COMMENTS

With the currently enrolling trials of VNS in Europe and the United States, there will likely be a significant increase in the availability of this technology. Medical centers need to prepare for this change, and this article helps create a valuable template for potential providers.

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