Vagus Nerve Stimulation (VNS) 5

Mario A. Cristancho, Pilar Cristancho,
Murat Altinay, and John P. O'Reardon

5.1 Introduction

Depression is a common, recurrent, and chronic disorder and as such is one of the leading contributors to disability globally [1]. Persistent and severe depression is also strongly linked to suicide which remains a leading cause of death for adolescents and young adults in the USA [2]. Despite the disability burden and the intimate links between depression and suicide, our current treatments including psychotropic

M.A. Cristancho, M.D. (✉)
Department of Psychiatry, Neuromodulation Treatment and Research Program, University of Pennsylvania, Philadelphia, PA, USA
e-mail: mario.cristancho@uphs.upenn.edu

P. Cristancho, M.D.
Department of Psychiatry, School of Medicine, Washington University in St. Louis, St. Louis, MO, USA

M. Altinay, M.D.
Department of Psychiatry and Psychology, The Cleveland Clinic Foundation, Cleveland, OH, USA

J.P. O'Reardon, M.D.
Department of Psychiatry, Center for Mood Disorders and Neuromodulation Therapies, University of Medicine and Dentistry SOM, Stratford, NJ, USA

J.A. Camprodon et al. (eds.), *Psychiatric Neurotherapeutics*, Current Clinical Psychiatry, DOI 10.1007/978-1-59745-495-7_5

medications, psychotherapy, and electroconvulsive therapy (ECT) fail to elicit adequate response in 20–40 % of cases [3]. The less than optimal outcomes observed in the state-of-the-art STAR-D clinical effectiveness trial sponsored by the NIMH highlighted these limitations [4]. Although ECT is highly effective as an acute treatment, it has a high relapse rate (50 % at 1 year) [5].

In response to this need for additional treatment options for the severely depressed patient, a new therapeutic field known as "neuromodulation" has gradually emerged. Vagus nerve stimulation (VNS) is an implantable neuromodulation device, which has established efficacy in medication-resistant epilepsy. It was approved by the US Food and Drug Administration (FDA) as an adjunctive treatment for severe, recurrent unipolar and bipolar depression in 2005 and has been investigated as a therapy for other disorders including anxiety, migraines, and Alzheimer's disease [6, 7].

The purpose of this chapter is to review the history and development of VNS, its efficacy and safety profile, and its current role in clinical practice as a treatment option for patients who suffer from severe depression.

5.2 History and Evidence

VNS was approved for treatment-resistant epilepsy in Europe in 1994 and in the United States (USA) in 1997 [7]. Anecdotal clinical observations of mood improvement in epilepsy patients after VNS implantation suggested a role for VNS therapy in depression and prompted further clinical investigation [6, 8, 9].

5.2.1 Mood Changes in Epilepsy Studies

An initial pilot prospective study of the effects of VNS on mood in epilepsy patients treated either with VNS or antiepileptic drugs showed mood improvement in the VNS group at 3 months. This improvement was not associated with reduction in seizure frequency [8]. Similar outcomes were reported by a separate independent study in a group of patients with epilepsy and mild depression

($n=11$). After VNS therapy, most patients with clinical significant depressive symptoms showed decreases in scores according to the Montgomery-Asberg Depression Rating Scale (MADRS) at 6 months. Interestingly, in terms of antiepileptic effect, only 2 out of the 11 patients were considered responders [9]. Those findings suggested that VNS has a separate and distinct effect on depressive symptoms not related to outcomes on seizures reduction [6, 8, 9].

5.2.2 Open-Label Studies in TRD

At least two pilot studies of VNS in treatment-resistant depression (TRD), with no history of epilepsy, have been carried out. The first trial included 30 patients with chronic unipolar or bipolar depression without psychotic features or rapid cycling. Patients had failed at least two adequate antidepressant trials and remained on their existing antidepressant treatments. A response rate of 40 % and a remission rate of 17 % were achieved after 10 weeks of VNS stimulation [6, 10].

A second report with a bigger sample (30 subjects from the initial sample plus 30 additional subjects all with TRD) showed a less robust effect after 10 weeks [11] with a response rate of 30 % on the 28-item Hamilton Depression Rating Scale (HAM-D), 37 % on the Clinical Global Impression of Improvement Scale (CGI-I), and 34 % on the MADRS. Remission (HAM-D score ≤ 10) rate was 15 %. Subjects in the second report appeared to have a more severe treatment-resistant course as evidenced by an average of 16 antidepressant treatment failures and about 40 % failure to respond to ECT in the current depressive episode [11]. The higher level of treatment resistance may have been responsible for the less favorable results in that sample. Nonetheless, under those circumstances, a response to VNS of 30–37 % indicated a therapeutic signal worthy of study under controlled conditions [6, 11].

These initial open-label studies limited the time of exposure to VNS to only 10 weeks. This is perhaps a short time to fully evaluate benefits of a long-term intervention. Marangell et al. [12] reported longer-term outcomes in the first cohort ($n=30$). They observed both increases in response rate from 40 to 46 % and increase in the remission rate from 17 to 29 % at the end of 12

months (9 months after completion of the initial 3 months acute phase treatment). Improvements in the level of patient's functioning were also noted. These authors pointed out that patients not only tolerated VNS well (91 % continuing to be responders) but also continued to improve over time [6, 12].

5.2.3 Results from the RCT of VNS in TRD

Rush et al. carried out the first randomized controlled study of VNS in patients with treatment-resistant depression [13]. They enrolled 225 patients from 21 different study sites and monitored results after 10 weeks of stimulation. Both the active group and the sham group were implanted with VNS, but only the active group had the device turned on. Patients in the active and sham group had equal number of visits, and sham adjustments were made in the sham group to preserve the blinding [13].

Unfortunately, this was a negative trial with a response rate of 15 % ($n=112$) on the 24-item HAM-D (primary outcome) and a response rate of 10 % in the sham arm ($n=110$) without reaching statistical significance ($p=0.238$) after 10 weeks. Only a secondary measure, the 30-item Inventory of Depression Symptoms (IDS-SR-30) indicated some benefit in the active group with a response rate of 17 % versus a response rate of 7 % in the sham group and statistical significance ($p=0.032$). A reassuring finding was the tolerability of the stimulation; in general patients tolerated it well and only 1 % of patients withdrew due to side effects [6, 13].

5.2.4 Longer-Term Outcomes with VNS versus Treatment as Usual

Following the 10-week randomized controlled trial and given the clinical suspicion that longer exposure to VNS could lead to better therapeutic effects, this cohort was followed in a 12-month naturalistic study [14], and significant reductions on the HAM-D 24 were observed over time. This measure decreased by 0.45 points per month (SE = 0.5) [14].

In light of the abovementioned findings, a standard comparison group was sought to better interpret outcomes with VNS. The comparison group was a group of depressed patients with chronic or treatment-resistant mood disorder. This group ($n=124$) was receiving "treatment as usual" (TAU) including medications, psychotherapy, or other somatic treatments (e.g., light therapy, electroconvulsive therapy, or transcranial magnetic stimulation) and was compared to a group of TRD patients who received VNS along with treatment as usual (VNS plus TAU, $n=205$) [15]. Clinical and health cost outcomes were prospectively followed for 12 months. This nonrandomized trial was conducted at 12 academic medical centers in the USA. The groups were comparable at baseline with highly similar characteristics. However, a few clinical and demographic characteristics differed at baseline including a greater proportion of previous depressive episodes in the TAU group, more exposure to ECT in the VNS plus TAU group, and slightly more ethnic minorities other than Caucasians in the TAU group [6, 15]. In both groups, most patients had a long history of illness (25 years), and the majority had a diagnosis of unipolar or bipolar depression. About 70 % were in a chronic depressive episode and had failed an average of 3.5 adequate antidepressant trials in the current episode. Baseline 24-item HAM-D mean scores were 28 for the VNS plus TAU group and 27.5 for the TAU group.

Subjects in the VNS plus TAU group had a greater reduction in the IDS-SR 30 scores (0.40) per month than the TAU group [SE = 0.10, $t(1092)=4.09$, $p<0.001$]. The IDS-SR indicated a response rate of 22 % for the VNS plus TAU group versus 15 % for the TAU group. The 24-item HAM-D showed a 30 % response rate in the VNS plus TAU group versus 13 % response in the TAU group. The CGI indicated a 37 % response rate in the VNS plus TAU group and a 12 % in the TAU group [6, 15]. The durability of effect of VNS was also analyzed, demonstrating that more than half of the responders (16 of 29) at 3 months continue to respond at 12 months in the VNS plus TAU group. On the contrary, only one of the seven responders to TAU at 3 months continues to respond at 12 months [15]. Overall these outcomes suggested that the use of adjunctive VNS increased the response rate in patients with treatment-resistant depression by 2–3-fold which, despite the

low absolute response rates, it implies an adjunctive benefit worthy of clinical consideration in patients with severe illness [6].

5.2.5 FDA Approval of VNS for TRD

In 2005 the FDA approved VNS as an adjunctive treatment for treatment-resistant depression. The FDA indication is limited to adult patients with chronic or recurrent unipolar or bipolar depression without psychotic features who have failed to respond to at least four previous antidepressants. The device should be implanted only by surgeons with experience operating within the carotid sheath, usually neurosurgeons or vascular surgeons. Patients should be followed by psychiatrists trained in programming the device and with expertise in treatment-resistant depression [6, 16].

Even though the FDA's approval of VNS represented another therapeutic option for patients with TRD, its approval was controversial, despite the safety, meaningful, and durable results observed over the long term. The failure of active VNS to separate from the sham control condition in the 12-week randomized control trial and the use of a matched control group instead of a randomized control group in the long-term data were sources of contention [6].

A main polemic point was the misunderstanding regarding the regulatory standards for approval of medical devices. The FDA's Medical Devices Amendment Act of 1976 defines the types of data to be used in support of safety and effectiveness for a given medical device. These include not only randomized controlled trials but also observational and epidemiological studies [17]. In addition, while for approval of medications the FDA requires two pivotal trials, one positive-controlled multicenter trial represents sufficient effectiveness evidence for medical devices. In the case of VNS, the one-year controlled trial of VNS plus TAU vs. TAU alone fulfilled this requirement [6].

Furthermore, prior to VNS, ECT was the only approved medical device used in TRD. In accordance with the FDA Modernization Act of 1997, treatments that address unmet medical needs, such as adequate treatment of TRD or antiretroviral agents for HIV infection, are eligible for fast-track approval. Manufacturers of treatments approved via the fast-track process are required to conduct

adequate follow-up studies to further characterize efficacy and safety [17]. Such a post-marketing study is currently ongoing for VNS in patients with treatment-resistant depression [18].

The controversy surrounding the FDA approval of VNS has impacted the availability and coverage for VNS therapy. In our own practice in the treatment-resistant depression clinic at an academic medical center, most insurance companies refuse coverage for VNS. In many cases, the therapy is considered "investigational" despite of the FDA approval. A cumbersome appeal process to the initial denial is necessary in the very limited cases that are finally approved [6].

5.3 VNS Basics

5.3.1 Vagus Nerve Anatomy

The vagus nerve exits the cranium through the jugular foramen and travels in the neck between the jugular vein and the carotid artery in the carotid sheath. The vagus nerve provides innervation to the larynx, esophagus, trachea, heart, aorta, and gastrointestinal organs [7, 19]. The right vagus has an important role on heart rate regulation as it innervates the sinoatrial node which is involved in the pace maker function of the heart.

The left vagus innervates the atrioventricular node having less influence in heart rate. It has been demonstrated that stimulation of the left vagus nerve, even at high levels, has no effect on heart rate [7]. Afferent fibers of the left vagus nerve bifurcate to innervate the nucleus tractus solitarius (NTS) bilaterally when they reach the brainstem. The NTS relays information to other brain regions such as the parabrachial nucleus (PBN), the cerebellum, the raphe nuclei, the periaqueductal gray matter (PAG), and the locus ceruleus, as well as to limbic, paralimbic, and cortical regions. The PBN relays information to the hypothalamus, thalamus, amygdala, and nucleus of the stria terminalis. Subsequently, the thalamus relays information to the insular, orbitofrontal, and prefrontal cortices, and other higher brain structures [19]. Vagal projections to the locus ceruleus and raphe nuclei are important because they contain noradrenergic and serotonergic projections, respectively,

implicated in the mechanism of action of traditional antidepressant medications [20].

5.3.2 Mechanism of Action in Depression

As in epilepsy, the mechanisms that mediate the beneficial effects of VNS therapy for depression are incompletely understood. However, evidence from neuroimaging and other studies suggests that VNS therapy adopts a bottom-up approach to modulating the neural circuitry of depression by stimulating vagal afferent fibers in the neck that innervates the NTS, and project rostrally to reach structures that are associated with the regulation of mood and emotions [19]. Functional magnetic resonance imaging (fMRI) studies have also explored VNS' mechanism of action [21–23]. Kosek et al. [22] used single-photon emission tomography (SPECT) to study depressed patients ($n = 15$) who received 10 weeks of VNS stimulation and showed that VNS caused increased regional cerebral blood flow (rCBF) in the left dorsolateral and ventrolateral prefrontal cortex (Brodmann areas 46 and 47) which are known to have decreased regional cerebral blood flow and glucose metabolism in patients with MDD [24]. These findings seem to be in line with the results of studies that assessed the effects of other neuromodulation therapies like the transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT) [22, 25]. Heterogeneous stimulation parameters, small sample sizes, and variable imaging methodologies result in significant limitations in order to draw conclusions regarding possible mechanisms of action, but hopefully further hypothesis-driven clinical and imaging studies will increase our understanding of the mechanisms of action of VNS in depression.

5.3.3 VNS Device Surgery

The VNS device consists of an implantable generator connected to electrodes that deliver low-frequency, chronic, intermittent-pulsed electrical signals to the left cervical vagus nerve (Fig. 5.1). The pulse generator is roughly the size of a pocket watch and is

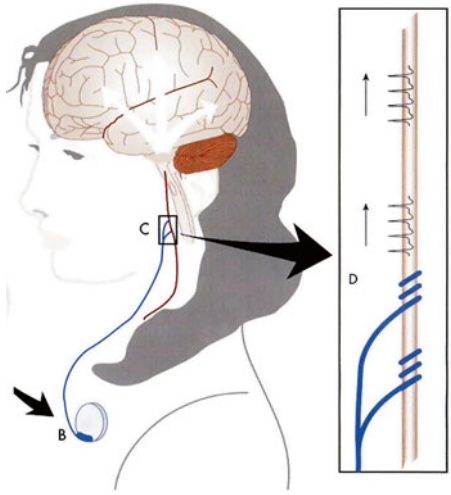

Fig. 5.1 The VNS device consists of an implantable generator that is connected to electrodes by a *thin* and flexible wire. It delivers electrical signals to the left cervical vagus nerve. Adapted from Higgins ES, George MS. Brain stimulation therapies for clinicians. Washington, DC, American Psychiatric Publishing, Inc. 2009

implanted subcutaneously in the anterior chest wall by a surgical procedure similar to a cardiac pacemaker implantation. Through a separate incision in the neck, the surgeon wraps the bipolar nerve-stimulating electrodes around the left cervical vagus nerve. Subsequently, the electrodes are connected to the implanted generator by a thin, flexible wire via a subcutaneous tunneling procedure [6, 19, 26, 27].

5.4 Managing Patients with VNS in the Office

5.4.1 VNS Device Programming

Psychiatrists manipulate the VNS device noninvasively by placing a programming wand over the site of the pulse generator implant. The programming wand is connected to a handheld computer with software installed that facilitates the adjustment of

stimulation parameters. Patients are supplied with a magnet that can be held over the generator to temporarily suspend stimulation, allowing immediate control over side effects if needed. Programmed stimulation resumes when the patient removes the magnet [6, 19, 26, 27].

5.4.1.1 Candidates for Therapy

VNS is an adjunctive option treatment for patients with unipolar or bipolar depression with a treatment-resistant course. Per FDA label, patients should have failed to respond to at least four adequate (in both duration and dose) trials of antidepressant medications [16]. Ideally but not required, patients should have had a trial of psychotherapy before considering adjunctive treatment with VNS [6].

A failed trial of ECT is not a requisite for VNS eligibility. In fact, given the different estimated time of improvement with these treatment modalities, it may be appropriate, in some cases, to use ECT acutely for severe symptoms followed by VNS as a long-term maintenance intervention [6]. Of note, the VNS device should be temporarily shut off while the patient received ECT and then restarted immediately after the procedure. Similarly, and due to its nonsystemic nature, VNS can be combined safely with antidepressant including MAOIs [6].

5.4.1.2 General Precautions and Contraindications

VNS is not approved for major depression with psychotic features or schizoaffective disorder. The presence of paranoid delusions would make placement of an implanted device not ideal. Unstable axis II conditions, such as borderline personality disorder, should be considered a relative contraindication because the patient may lack sufficient stability to comply with the demands of a surgical intervention, frequent follow-up, and slow trajectory of response. VNS has not been studied during pregnancy. However, given that it is a nonsystemic treatment, one might assume that it has a very limited effect on the fetus [6].

Both patients and physicians should be aware that MRIs are contraindicated. Nonetheless, by using special send-receive coils, it is still possible to obtain an MRI of the brain; otherwise, a CT scan should be used instead of an MRI [6].

If VNS fails to provide clinical improvement, the device can be switched off and be left in place. Other options include explantation of the pulse generator; however, it is generally recommended that the electrode (attached to vagus nerve) remains in situ because of concerns that adhesions around the vagus nerve might increase the risk of nerve injury during the removal procedure. If the electrodes remain in situ, the MRI-associated precautions remain in effect. Other devices such as cell phones, microwave ovens, or airport security systems should not have any adverse effects on functioning of the VNS device [6].

5.4.2 Dosing Parameters

During the office follow-up visits, the psychiatrist assesses the clinical progress, monitors side effects, and performs adjustments of the stimulation. Actual adjustment of the stimulation settings usually takes about 10 min. The patient holds a programming wand over the implanted pulse generator (on the skin or thin layer of cloth), and the clinician interrogates the device by means of a handheld computer. Four principal settings are adjusted: current charge (mA), pulse width (microseconds), frequency (Hz), and duty cycle (percentage the device is on/off) [6].

***Current Charge*:** Patients are generally started at 0.25 mA, which is then gradually increased in 0.25 mA increments while maintaining a comfortable tolerance level [6]. Indication that the maximum tolerable level has been reached/exceeded is immediately obvious, as the patient will report significant discomfort or cough. Current dosing ranges from 0.25 to 3.5 mA [6]. The median dose in the 12-month pivotal trial was 1.0 mA [15].

***Frequency and Pulse Width*:** Frequency ranges from 1 to 30 Hz and a typical value is 20 Hz. Stimulation frequencies of 50 Hz and above can cause major irreversible damage to the vagus nerve [7]. Pulse width ranges from 130 to 1000 μs and a typical value is 500 μs [6]. Pulse width of 130 μs is less frequently used because they are thought to be subtherapeutic.

***Duty Cycle*:** It refers to the on-time relative to off-time of the stimulation in seconds, and it is expressed as a percentage. The stimulus on-time ranges from 7 to 60 s with a typical value of 30 s. The off-time can be set anywhere from 0.2 to 180 min, and a typical value is 5 min [6]. Tables for easy and safe adjustment of duty cycle are available and should be provided by the manufacturer.

The first dosing visit is done about 2 weeks post surgery to allow for healing of the tissue postoperatively. Weekly visits are recommended for the first month to closely monitor tolerance and mood changes. Initial titrations occur at 0.25 mA increments in current so that a target dose of 1.0 mA is achieved after a month. Subsequent visits can be conducted every 2 weeks and then spaced to once a month if there is sustained clinical improvement. By 3 months, if the current amplitude is optimal in the range of 1.0–1.5 mA but the patient has not improved, then the duty cycle can be increased. A significant proportion of responders to VNS only emerge in the second 6 months of stimulation. A full VNS trial may require up to a year [6].

5.5 VNS Effectiveness in Clinical Practice Post: FDA Approval

Research data on long-term efficacy lead to the FDA approval of VNS. However, how these research results translate into clinical practice was an important question to address. This background question led our group to publish the one-year clinical outcomes under routine clinical circumstances in our patients ($n=15$) who received VNS implants for depression in the first 18 months after the FDA *approval* [28]. This small investigation included 10 patients with major depression and 5 patients with bipolar depression. All patients received VNS implants for severe depression with previous nonresponse to a minimum of four antidepressant trials. VNS was used as an adjunct to existing medications. Results showed a statistically significant decrease in the Beck Depression Inventory (BDI) after VNS therapy, from a baseline mean score of 37.8 (SD = 7.8) (severe depression) to a mean score of 24.69 (SD = 11.4) (moderate depression) ($p<0.01$). Response rate and remission rates were 28.6 % and 7 %, respectively, according to

the BDI. Secondary outcomes such as the HAM-D 24 indicated a 43 % response rate and a 21.4 % remission rate. We attributed the numerically lower rates in the BDI (a self-reported measure) compared to the HDRS to the fact that depressed patients may be less aware of their improvement due to their negative perception or pessimism as a core feature of their illness [28].

We also directly compared our one-year clinical response rates to those previously reported in efficacy trials after one year [28]. We observed that according to the HAM-D (the most commonly used scale in clinical trials), our patients' response rate of 43 % fell in between a 46 % response rate previously reported by Marangell et al. [12] in an open-label VNS trial and 30 % response rate from the pivotal VNS plus treatment as usual (TAU) trial by George et al. [15].

Interestingly, our VNS cohort had more prior exposure to ECT, greater number of lifetime major depressive episodes, and higher number of previous suicide attempts and hospitalizations compared to that of subjects in the VNS plus TAU study patients [15]. Nevertheless their clinical improvement was significant. We also compared categorical outcomes on the HDRS—24 items end-point scores at one year between our study and the pivotal VNS with TAU trial and found no statistically significant differences in outcomes in between our results and that trial [28]. Thus, this effectiveness study found comparable results in standard clinical practice with VNS as in the research trials even though the cohort of clinic patients was a relatively more severe TRD patient population.

5.6 Safety and Tolerability

5.6.1 Surgery Complications

Pain and wound infection are the most common surgical complications. Wound infection occurred in about 3–6 % of patients in the clinical trials and although generally were managed with antibiotics, removal of the device has been required in rare occasions. Transient left vocal cord paresis has been reported. Most worrisome but rare asystole has occurred in the operating room during lead testing in 1 per 1000 implants. No deaths have been reported due to surgical implantation [6, 29].

5.6.2 Side Effects Related to Stimulation

Side effects related to the stimulation are the most common. Patients experience them only while the stimulation is on. They are generally mild and related to the intensity of the output current with hoarseness, dyspnea, and cough being the most commonly reported. Side effects tend to decrease over time, although hoarseness persists in about 27–54 % cases [6, 15, 29].

5.6.3 Psychiatric Adverse Events

Treatment emergent hypomania (1.2 %) and mania (1.2 %) have been reported with VNS. They have occurred mostly in bipolar patients, and in most cases VNS has been continued safely after resolution of symptoms [6, 14].

Another important outcome for any antidepressant treatment is the risk of suicidal ideation and suicidal behavior. For VNS therapy, the pivotal trial adjunctive VNS vs. TAU defined treatment emergent suicidality as a two-point increase on the suicide item of the HAM-D 24. The rate of treatment emergent suicidality was 3 % for the VNS group (5/181) and 2 % (2/184) for the TAU group. The difference was not statistically significant; therefore, there is no suggestion that VNS would specifically exacerbate suicidality [6, 30].

The risk of suicidal behavior was summarized in the executive summary and discussion of the VNS therapy indication for depression presented to the FDA. This summary estimated the rate of suicide attempts in the combined VNS studies in TRD ($n = 345$) to be 3.5 % per patient year. A patient year was defined as one subject receiving VNS therapy for 12 months [30]. This rate is very similar to that described by Khan et al. [31], who reported a 3.4 % suicide attempt rate in a review of 45 studies of major depression comprising 7 standard antidepressant medications (fluoxetine, sertraline, paroxetine, nefazodone, mirtazapine, bupropion, and venlafaxine) in nearly 20,000 patients. Likewise, the rate for completed suicides for the combined VNS studies was 0.4 % patients per

year, which is also comparable to a 0.7 % suicide rate reported by Khan et al. on antidepressants [31]. These data suggest that VNS does not possess an increase in suicidal risks superior to that of antidepressants [6, 30].

Finally, no cognitive side effects have been reported with VNS, but to the contrary, a trend toward improvement in cognitive functions was reported by Sackeim et al. [6, 32].

5.6.4 Adherence to Treatment

Rush et al. reported a 90 % continuation rate of VNS therapy after a year. Side effects were responsible for a 3 % discontinuation rate. The remaining patients discontinued to lack of efficacy [14]. This rate decreased at 2 years with an adherence of 80 % to treatment as reported by Nahas et al. [33]. The expected battery life for this device is 5–10 years, after which surgical replacement of the battery can be pursued.

5.7 Summary

Well established data supports VNS's efficacy and safety in TRD. Nevertheless, it is not devoid of limitations including the fact that the randomized controlled trial over 12 weeks was a negative study. However, results from a controlled post-marketing study as suggested by the FDA (results expected in 2012) may help clarify VNS' role in depression and will likely determine its future as a neuromodulation treatment option in TRD [18].

In the interim unfortunately, there is very limited access to VNS for patients, despite FDA approval. The recent decision by Centers for Medicare and Medicaid Services (CMS) on behalf of Medicare to not cover the costs of VNS implants in TRD has been a major deterrent to the coverage of VNS by all insurance companies, as a reasonable therapeutic option even in the most refractory cases of depression.

References

1. Murray C, Lopez A. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. Cambridge, MA: Harcourt University Press; 1996.
2. Centers for Disease Control and Prevention (CDC). Web-based inquiry statistics query and reporting system (WISQARS) (online). National Center for Injury Prevention and Control, CDD (producer). Available from www.cdc.gov/injury/wisqars/index.html. 2010.
3. Sackeim HA. The definition and meaning of treatment-resistant depression. J Clin Psychiatry. 2001;16:10–7.
4. Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewki SR. The STARD project results: a comprehensive review of findings. Curr Psychiatry Rep. 2007;9(6):449–59.
5. Tew Jr JD, Mulsant BH, Haskett RF, Joan P, Begley AE, Sackeim HA. Relapse during continuation pharmacotherapy after acute response to ECT: a comparison of usual care versus protocolized treatment. J Clin Psychiatry. 2007;19(1):1–4.
6. O'Reardon JP, Cristancho P, Peshek A. Vagus nerve stimulation (VNS) and treatment of depression: to the brainstem and beyond. Psychiatry. 2006;3(5):4–63.
7. Groves DA, Brown VJ. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neurosci Biobehav Rev. 2005;29:493–500.
8. Harden CL, Pulver MC, Ravdin LD, Nikolov B, Halper JP, Labar DR. A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. Epilepsy Behav. 2000;1(2):93–9.
9. Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res. 2000;42:203–10.
10. Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. Biol Psychiatry. 2000;47:276–86.
11. Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. Neuropsychopharmacology. 2001;25:713–28.
12. Marangell LB, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. Biol Psychiatry. 2002;51:280–7.
13. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry. 2005;58:347–54.
14. Rush AJ, Sackeim HA, Marangell LB, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. Biol Psychiatry. 2005;58:355–63.

15. George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry. 2005;58:364–73.
16. http://www.accessdata.fda.gov/cdrh_docs/pdf/p970003s050a.pdf
17. Maisel M. Medical device regulation: an introduction for the practicing physician. Ann Intern Med. 2004;146:296–302.
18. http:clinicaltrials.gov/ct2/show/study/NCT00305565?term=vagus+nerve+stimulation+depression&rank=7&show_locs=Y#locn
19. Nemeroff CB, Mayberg HS, Krahl SE, et al. VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. Neuropsychopharmacology. 2006;31:1345–55.
20. Lenox RH, Frazer A. Mechanism of action of antidepressants and mood stabilizers (chapter 79). In: Davis KL, Charney D, Coyle JT, Nemeroftt C, editors. Neuropsychopharmacology: the fifth generation of progress. Lippincott Williams and Wilkins: Philadelphia; 2002. p. 1139–63.
21. Lomarev MP, Denslow S, Nahas Z, Chae JH, George MS, Bohning DE. Vagus nerve stimulation (VNS) synchronized BOLD fMRI suggests that VNS in depressed adults has frequency/dose dependent effects. J Psychiatr Res. 2002;36:219–27.
22. Kosel M, Brockmann H, Frick C, Zobel A, Schlaepfer T. Chronic vagus nerve stimulation for treatment-resistant depression increases regional blood flow in the dorsolateral prefrontal cortex. Psychiatry Res Neuroimaging. 2011;191:153–9.
23. Conway CR, Sheline YI, Chibnall JT, George MS, Fletcher JW, Mintun MA. Cerebral blood flow changes during vagus nerve stimulation for depression. Psychiatry Res. 2006;146:179–84.
24. Dougherty DD, Rauch SL. Brain correlates of antidepressant treatment outcome from neuroimaging studies in depression. Psychiatr Clin N Am. 2007;30:91–103.
25. Nobler MS, Oquendo MA, Kegeles LS, Malone KM, Campbell CC, Sackeim HA, Mann JJ. Decreased regional brain metabolism after ECT. Am J Psychiatry. 2001;158:305–8.
26. George MS, Nahas Z, Bohning DE, et al. Mechanism of action of VNS. Clin Neurosci Res. 2004;4:71–9.
27. Matthews K, Eljamel MS. Vagus nerve stimulation and refractory depression. Br J Psychiatr. 2003;183:181–3.
28. Cristancho P, Cristancho MA, Baltuch GH, Thase ME, O'Reardon JP. Effectiveness and safety of vagus nerve stimulation for severe treatment resistant major depression in clinical practice after FDA approval: outcomes at one year. J Clin Psychiatry. 2011;72(10):1376–82.
29. Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. J Clin Neurophysiol. 2001;18:415–8.
30. Rudolph R. Food and Drug Administration Neurological Devices Panel Web site. Executive summary and discussion of the vagus nerve stimulation (VNS) therapy depression indication clinical data (updated to include information from deficiency letter response). http://www.fda.gov/ohrms/

dockets/ac/04/briefing/4047b1_01_Clinical%20Executive%20Summary-FINAL.pdf. 2005.
31. Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials. Arch Gen Psychiatry. 2000;57:311–7.
32. Sackeim HA, Keilp JG, Rush AJ, et al. The effects of vagus nerve stimulation on cognitive performance in patients with treatment-resistant depression. Neuropsychiatr Neuropsychol Behav Neurol. 2001;14:53–62.
33. Nahas Z, Marangell LB, Husain MM, et al. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. J Clin Psychiatry. 2005;66:1097–104.