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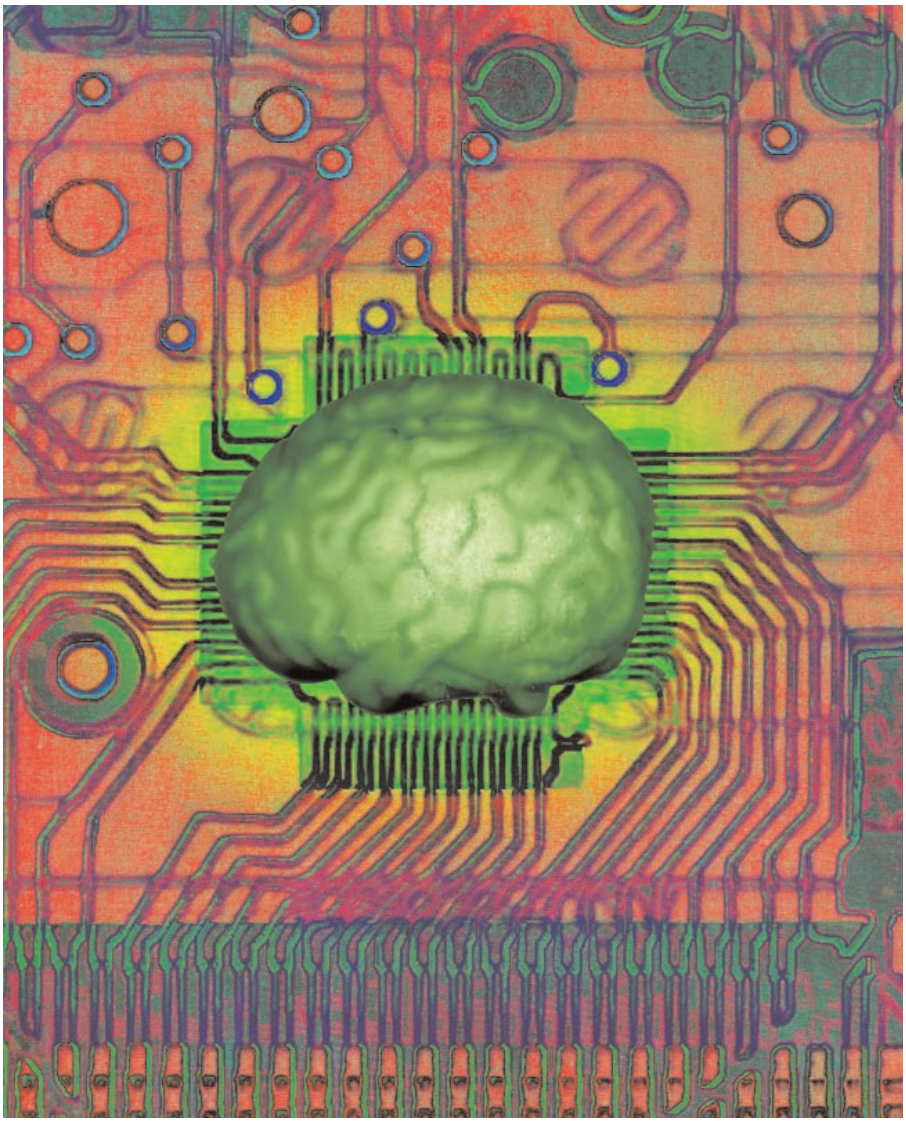
Vagus Nerve Stimulation (VNS) and Treatment of Depression: To the Brainstem and Beyond

DISCLOSURE: Dr. O'Reardon has received research support from and is on the speakers bureau for Cyberonics.

ABSTRACT

Neuromodulation appears to be emerging gradually as a new therapeutic field in psychiatric treatment. It encompasses neuropsychiatric medical devices, such as vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), and electroconvulsive therapy (ECT). As a therapeutic approach to affective disorders, neuromodulation shifts the focus from the monoamine synapse to neural circuitry of the brain, which is dysregulated in depression. This neural circuitry has been elaborated on over the course of 15 years of neuroimaging research in mood disorders and is now believed to encompass disturbances in a frontolimbic network. These include reduced metabolism and blood flow in the prefrontal cortex and anterior cingulate and pathologically increased activity in the subgenual cingulate and amygdala.

VNS is an implanted device that has established efficacy in pharmaco-resistant epilepsy. It was approved by the FDA for the treatment of severe, recurrent unipolar and bipolar depression in July of 2005. VNS adopts a bottom-up approach to modulating the neural circuitry of depression by stimulating vagal afferent fibers in the neck, which carry impulses to the brain stem to target there the locus ceruleus and dorsal raphe nucleus. Now that VNS has moved beyond the experimental phase and into the clinic, psychiatrists are faced with deciding who is an



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appropriate patient for this surgical implant and how to integrate VNS into existing treatment in order to optimize both efficacy and safety.

This review of VNS will assess the efficacy and safety data that led to the FDA approval. We will also review for the busy clinician how VNS is likely to translate into clinical practice as a treatment option for patients in need who are suffering from severe depression.

LIMITATIONS OF EXISTING TREATMENTS FOR CLINICAL DEPRESSION

Failures of episodes of depression to respond satisfactorily to our currently available treatment options is a major clinical and societal problem. Depression, be it bipolar or unipolar in origin, is a common, recurrent, and frequently 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 the primary disease-based killer of young people aged 15 to 40 years old in the US. Despite the disability burden and the intimate links between depression and suicide, our current treatments fall far short of the ideal, with an estimated 20 to 40 percent failing to respond adequately to repeated trials of antidepressant interventions.[2]

STAR-D OUTCOMES

The results of the first phase of the STAR-D (Sequenced Treatment Alternatives to Relieve Depression) program, which were published recently, are illustrative in this regard.[3] A very large sample of outpatients with major depression (n=2,876), which was designed to be representative of the average clinical population in terms of severity and comorbidity, was treated with citalopram at optimized dosing for a full course of 8 to 12 weeks. Although almost 70 percent of patients achieved a dose of citalopram of 40mg or higher, the ultimate response rate at study endpoint fell below half (47%), and the remission rate achieved was only 28 percent.

PSYCHOTHERAPY

Depression-specific therapies, such as cognitive behavioral therapy (CBT), when conducted at centers of excellence have produced response rates in outpatient major depression of 45 percent at eight weeks and 58 percent at 16 weeks, indicating that a substantial subgroup do not benefit from CBT even when this psychotherapy modality is administered with a high level of expertise, a level of expertise that may not be readily reproducible in more standard clinical settings.[4]

ELECTROCONVULSIVE THERAPY

Our best validated treatment for treatment-resistant depression (TRD) is electroconvulsive therapy (ECT) with documented acute response rates from the most recent large scale trial with bilateral ECT of 79 percent, and an equally impressive remission rate of 75 percent.[5] When ECT is administered in community rather than research settings, however, response rates drop down to 64 percent and remission rates fall to 47 percent.[6] In addition, despite scientific advances in technique and administration, stigmatization of ECT remains entrenched. When patient reluctance to undergo ECT due to stigma is combined with some legitimate concerns regarding adverse effects of ECT on memory function, it means that our most effective treatment for severe depression is and will likely continue to be a much underutilized one.

EMERGING TREATMENT ALTERNATIVES AND NEUROMODULATION

Given all of the above, there is a clear need for additional treatment options for the severely depressed patient group. An emerging therapeutic field with significant promise for affective disorders is what has been termed *neuromodulation*. This involves the application of medical device type technologies to modulate neural networks in the brain so to achieve sustained therapeutic effects beyond the session itself. ECT was the first psychiatric device to be used widely in this regard.

In the January issue of *Psychiatry 2006*, we reviewed the evidence suggesting that pulsed magnetic fields when administered via transcranial magnetic stimulation (TMS) may be effective in treating major depression and other psychiatric disorders. This month, we review the evidence that led to the approval of vagus nerve stimulation (VNS) by the Food and Drug Administration (FDA) in 2005 as an adjunctive treatment for chronic and recurrent depression, and we will assess what role VNS will likely play in clinical practice. Figures 1 and 2 illustrate the attachment of the device to the vagus nerve and the pulse generator and electorde components of the VNS therapy system.

Twenty to 40 percent of depressed patients fail to respond adequately to our current treatments.

HISTORY OF VNS IN PSYCHIATRY

Early antidepressant signals. VNS was approved for pharmacoresistant epilepsy in Europe in 1994 and in the US in 1997.[7] Anecdotal clinical observations of mood improvement in epilepsy patients, even in the absence of better control of seizures after VNS implantation, led to a pilot prospective study of VNS effects on mood in epilepsy patients, treated either with the VNS device or anti-epileptic drugs. Significant mood improvement was found in the VNS group at three months, which appeared to be independent of any improvement in seizure control, suggesting that VNS was having a separate and distinct effect on depressive symptoms.[8] The same finding was independently reported in a European study at about the same time with a group of epilepsy patients (n=11) with mild depression. Following VNS implantation, the proportion of patients with clinically significant depression on the Montgomery Asberg Depression Rating Scale (MADRS)(i.e., score above 10) fell from 9 out of 11 at baseline to only 2 out of 10 at the six-month follow up. In contrast, only 2 of 11 subjects in the trial could be classified as responders in terms of seizure reduction over the six months.[9]

Neurobiology of VNS. More than 50 years ago, animal experimentation revealed the following two findings: 1) VNS can induce synchronization of orbito-frontal activity on the EEG; and 2) VNS can induce emergence of frontal slow waves (a clinical marker of ECT efficacy)—both of which appear to have presaged its ultimate clinical applications.[7] More recently, Krahl, et al.,[10] showed that lesioning of the locus ceruleus bilaterally prevented VNS from blocking the induction of seizures in rats by electroshock, indicating that its anticonvulsant effects had a strong noradrenergic basis. In humans, chronic VNS in epileptic patients has been shown to be associated with elevation of the serotonin metabolite 5-hydroxyindolacetic acid and GABA levels in the CSF.[11]

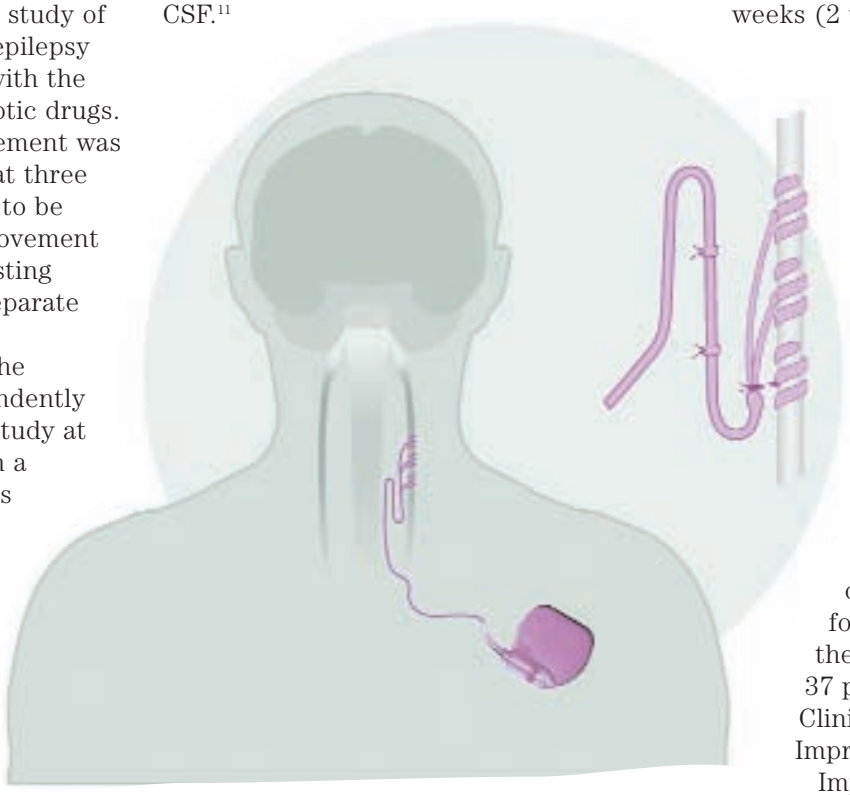

FIGURE 1. Schematic illustrating implanted pulse generator in chest wall and electrode attached to the left vagus nerve in the neck

PILOT STUDIES IN DEPRESSION

In light of the above, two pilot studies were conducted with VNS in patients with well characterized TRD. The first trial enrolled 30 patients with major depression or bipolar I or bipolar II disorder in a major depressive episode of at least a two-year duration (i.e., chronic) who had failed at least two research-adequate antidepressant trials. Patients with a rapid-cycling bipolar course or psychotic depression were excluded. Following surgical implantation and a two-week recovery period of no stimulation, 10 weeks of stimulation was applied in combination with continuation of the existing fixed medication regime. Results at 10-weeks were promising with a response rate of 40 percent and a full recovery or remission rate of 17 percent.[12]

The second pilot study combined the initial study cohort with a further 30 TRD unipolar and bipolar patients for a total sample size of 60. This cohort of 60 patients was followed for 12 weeks (2 week recovery post-surgery without stimulation and then 10 weeks of VNS to determine the acute response to VNS). The results for the full sample were less promising than the first trial with a response rate on this occasion for 30 percent on the 28-item HAM-D, 37 percent on the Clinical Global Impression of Improvement Scale (CGI-I), and 34 percent on the MADRS. Remission (as defined by 28-item HAM-D score <10) was seen in 15 percent of patients in the study. The higher degree of treatment resistance in the second pilot study as compared to the first appears to have been a significant factor in the less favorable outcome. Patients who had never received ECT (lifetime) were found to be much more likely to respond to VNS, by a factor of four. In addition, none of the 13 patients who had failed more than seven adequate antidepressant trials in the current episode responded (0% response rate) versus a response rate of 39 percent in the remaining subjects.[13]

It should be emphasized that the

cohort of TRD patients studied in these first trials of VNS were severely ill and would have been routinely excluded from antidepressant or psychotherapy clinical trials. The median duration of the current depressive episode was seven years, and patients had failed to respond to 16 distinct medication interventions in the episode. The average lifetime duration of affective illness was 18 years. Two-thirds of the sample had received ECT in the past, and close to 40 percent had already failed ECT in the current episode. With this illness background, an overall response rate in the region of 30 to 37 percent (30% on the 28-item HAM-D and 37% on the CGI-I)[13] depending on outcome measure selected clearly would be deemed quite respectable and worthy of further study.

CONTROLLED PIVOTAL TRIAL OF VNS IN TRD

The results of the first large-scale controlled multicenter trial of VNS (n=225) were reported by Rush, et al., and were disappointing overall.[14] Active VNS was compared with a VNS sham stimulation condition in which both groups were implanted with the VNS device, but only the active group had the device turned on after recovery from surgery. Both groups had the same frequency of clinic visits and programming maneuvers with the device with the exception that in the sham group the current amplitude remained at 0mA. Subjects were told that they might or might not be aware of the stimulus, depending on individual sensitivity, and study raters were blind to device activation status. While it is correct that the group receiving active stimulation had a higher rate of hoarseness during the stimulus period compared to the sham group, meaning that perfect blinding of the patient was not possible, this was mitigated against by having the device shut off for both groups before rating sessions were completed so that the blind would be preserved as tightly as possible for the objective raters during conduct of actual ratings.

Outcomes. After 10 weeks of active stimulation, the response rate on the primary outcome measure (24-item HAM-D) was 15 percent (n=112) and the sham/placebo response was 10 percent (n=110), which did not differ from each other (p=0.238). Likewise, VNS showed no advantage over placebo in 2 out of the 3 secondary outcome measures (MADRS, CGI-I), indicative of absence of a signal of true benefit from VNS in this time course of stimulation.

On the self report measure (30-item Inventory of Depression Symptoms—IDS-SR-30), VNS did a little better with a response rate of 17 percent (versus 7% with sham/placebo) and significance was achieved (p=0.032). One other positive from the trial was the favorable tolerability of VNS, with a withdrawal rate of only one percent due to adverse events.[14]

In 2005, the FDA approved VNS for patients with depression, unipolar and bipolar, failing to respond to four or more antidepressant treatments

ONE YEAR OUTCOME WITH VNS COMPARED TO TREATMENT AS USUAL

The first pilot study of VNS in TRD described above[12] had followed patients (n=30) over the longer term and found that response rates tended to increase over time, indicating that 10-week trials of VNS might underestimate its potential to treat TRD patients. Marangell, et al., reported that following an additional nine months of VNS (1 year total) the response rate was sustained, with in fact a slight increase from 40 to 46 percent, and the remission rate increased from 17 percent at three months to 29 percent at one year.[15]

This led to the device manufacturer, in its submission to the FDA that sought approval for VNS as a novel treatment for TRD, to rely heavily on the one-year outcomes from its pivotal trial rather than the failed acute trial.[16] The submission to the FDA contrasted the one-year outcome in TRD with VNS to treatment as usual (TAU) for TRD in a comparison group of patients conducted at 12 academic medical centers in the US.[17] This was a nonrandomized comparison but nevertheless the TAU group (n=124) did not differ from the VNS group (n=205) in terms of illness characteristics.

Both groups had a lifetime duration of affective illness of 25 years and had been in the current depressive episode for a period of four to six years. Both groups had failed, on average, four research-adequate antidepressant trials in the current episode, and in about 70 percent of cases in both groups the episode was chronic in duration (>2 years). The baseline scores on the 24-item HAM-D were virtually identical at baseline (28 vs. 27.5) but notably the VNS group had histories indicative of less

responsiveness to ECT, and thus likely a more severe course of illness.

Outcomes. At the one-year mark, the TRD group who received adjunctive VNS had better outcomes compared to TAU only. On the HAM-D, the response rate with VNS was 30 percent versus 13 percent with TAU, and on the CGI-I the margin of superiority was greater (37% vs. 12% response rate). On the patient self report, IDS-SR-30, the response rate with VNS was 22 percent versus 12 percent for TAU. Thus, it could be argued that over the longer term, adjunctive VNS increased the response rate in TRD by 2- to 3-fold, which despite the fairly low absolute response rates, indicates impressive adjunctive benefit from VNS in this severely ill patient group.

FIGURE 2.
VNS system with pulse generator (2" diameter and 2oz weight) and electrode lead with helical windings that the surgeon wraps around the left vagus nerve

TWO-YEAR FOLLOW-UP DATA WITH VNS IN TRD

To date, the longitudinal follow-up with VNS in TRD patients is limited to two years. At the end of two years, the results remain substantially similar to that observed at one year. Nahas, et al., recently reported the long-term results from the pilot studies of VNS in TRD (n=59).[18] At two years, the response rate was 42 percent and the remission rate was 22 percent. VNS was well tolerated over the longer term, and 81 percent of the group originally implanted still had the device active at the two-year mark. The overall response rate of 40 to 45 percent long term (<50% reduction in depressive symptoms) contrasts with the 81 percent who still have the device active at two years. This is likely related to the fact that about an additional 25 percent of patients, separate from the 42 percent who are responders at two years, have an improvement in symptoms of somewhere between 25 and 49 percent, which is short of responder status, but perhaps meaningful in the context of severe, unremitting depression.

FDA APPROVAL FOR VNS IN TRD

In July, 2005, the status of VNS in the US moved beyond experimental and investigational and became a standard available option for clinicians with TRD patients following FDA approval. The FDA approved the VNS implant for patients with chronic or recurrent depression, either unipolar or bipolar, with a history of failure of the depression to respond to at least four antidepressant interventions. Patients are not required to have failed ECT to be eligible for VNS. It is not approved for psychotic depression and is only approved for adults 18 years of age and older. Surgeons who implant the device should be experienced in operating within the carotid sheath (usually neurosurgeons or vascular surgeons), and psychiatrists who program the VNS device are required to have training in programming it and be experienced in the management of TRD patients.

Controversy concerning FDA approval for VNS. The FDA approval for VNS as a long-term adjunctive treatment for TRD has not been without controversy, despite the documented safety of the procedure, and this largely stems from unresolved questions on its efficacy and an misunderstanding of the regulatory requirements for approval of medical devices, such as VNS, versus drugs. For instance, in January of 2006, the respected *Carlat Report on Psychiatric Treatment* responded to the pivotal trial and the FDA approval of VNS by stating, "Whether the study actually demonstrated anything at all about VNS efficacy is a topic that will likely be debated for years, and which we suspect will go down in the annals as one of the FDA's major embarrassments… Time will tell. VNS may indeed be effective for TRD. However, we believe that the FDA should not have approved VNS without its usual requirement of two positive, double-blind, placebo-controlled studies."[19] The mainstream media has also not been slow to highlight the fact that the approval for VNS was based on the FDA's interpretation of the long-term efficacy data with VNS, and came in spite of the failed short-term sham/placebo-controlled trial.[20]

Impact of controversy on access to VNS for TRD patients. This controversy, unfortunately, has been a boon to the insurance carriers who determine whether or not eligible patients, per FDA approval criteria, receive the procedure on their psychiatrists' recommendations. To date in our own VNS clinic, only 35 percent of TRD patients who are clearly appropriate for the procedure with most having already failed ECT, have been able to get the implant approved (7 out of 20 referrals for surgery, unpublished observations).

Routinely to date, patients are denied by their insurance carrier for VNS on the basis that the implant is deemed "experimental/investigational" despite the FDA approval. For now, the only real hope for patients in getting the VNS device implanted rests in a lengthy appeal process with the individual insurance company, although it is likely, though not guaranteed, in the long term with patient advocacy that insurance companies will honor the FDA approval of VNS.

Addressing critiques of FDA approval of VNS in depression. *1. Two positive multicenter trials with VNS should have been required.* This misunderstands the regulatory standards for approval of medical devices in the US. While it is true that the FDA requires two pivotal trials for drug approval, the regulations covering medical devices are somewhat different. Medical devices are generally more specifically targeted in the body than drugs and due to the nature of the conditions for which they are used the risk-benefit equation often differs from that of drugs. Thus the FDA, under the Medical Devices Amendment Act of 1976, is allowed to consider a range of data in support of safety and effectiveness, such as randomized controlled trials and observational and epidemiological studies.[21] Therefore, many medical devices have been approved by the FDA on the basis of scientific evidence other the classic randomized, placebo-controlled clinical trials.[16] In respect of medical devices, generally one positive, controlled, multicenter trial is accepted by the FDA as sufficient evidence of effectiveness, as was the case with VNS in respect on the one year comparator trial.

2. Standards applied by the FDA for VNS approval were insufficient. Clearly, the FDA relied on the long-term outcome data with VNS compared to TAU. The long-term data did not have the merit of having a sham/placebo comparison due to ethical limitations of a prolonged placebo condition in this population of patients, but was controlled in terms of a matched TAU group. A comparison with standards for medical device approval in Europe may be instructive in this regard. In Europe, where VNS was approved for depression in 2001, the standards for approval of a medical device are in fact less stringent. European Union standards require that the medical device be demonstrated to be safe in its intended usage, but whether the device is effective for an individual patient with a specific medical condition is left to the discretion of the patient and the physician.[22]

3. Level of efficacy of VNS is insufficient to be clinically of value. It is true that, in general, for any intervention and, in particular, one requiring surgery, one would like a level of efficacy in excess of 50 percent, which proves a certain psychological comfort for both patient and physician. However, this is unfortunately a naïve and unrealistic expectation in the setting of severe TRD, analogous to expecting a newly adopted chemotherapy to deliver remission rates in excess of 50 percent in patients with advanced cancer. The only fair comparison is with the benefit that standard available treatment or TAU can be expected to provide. In the case of VNS, the relative advantage of adjunctive VNS compared to TAU was a 2- to 3-fold improvement in response, albeit the absolute response rate still fell below 50 percent.[17] Given that almost 40 percent of these TRD patients had already failed an adequate trial of ECT in the current episode, a response rate of 30 to 37 percent at one year was clearly an advance on TAU.

SAFETY AND TOLERABILITY OF VNS

Surgery complications. Complications related to surgery are uncommon but include some risk of infection and pain at the incision site. Wound infection occurred in about three percent of cases in the TRD and epilepsy trials and were managed with oral antibiotics ordinarily. Only very rarely was device removal required in this instance.[23] Pain at the incision site usually resolves quickly within 1 to 2 weeks.[13] Problems, such as transient left vocal cord paresis, are related to surgical technique and usually resolve slowly over a period of weeks.[23] Asystole is a rare but clearly serious adverse event occurring in 1 per 1,000 implants in the operating room during initial lead testing. It may be related to arcing within the surgery field in the context of inadequate hemostatic control. No deaths have resulted, fortunately, and subsequently patients have been able to safely use VNS postoperatively.

FDA approval for VNS in depression rested on the long-term outcome data, which had a nonrandomized active control group rather than a sham/placebo control.

TABLE 1. Profile of adverse events seen with VNS in short term and long term trials

Adverse event	Sackeim, et al., 2001 *n*=60 10 weeks	Rush, et al., 2005 *n*=119 10 weeks	Rush, et al., 2005 *n*=209 12 months	Nahas, et al., 2005 *n*=59 24 months
Hoarseness	55%	68%	54%	27%
Cough	17%	29%	6%	--
Dyspnea	15%	23%	16%	8%
Neck pain	17%	21%	13%	13%
Pain	13%	--	6%	--
Headache	22%	--	4%	--
Dysphagia	13%	21%	4%	--
Vomiting	--	21%	--	--
Nausea	7%	--	2%	--
Dyspepsia	10%	10%	16%	--
Palpitations	5%	5%	--	--
Paresthesiae	7%	16%	4%	--
Laryngismus	--	11%	5%	--
Pharyngitis	13%	---	5%	--

Side effects related to stimulation. The more common VNS adverse events are those related to stimulation and, thus, are only experienced by the patient during the stimulation on time. The typical side effects reported during both acute phase and longer-term follow up studies in the TRD population, were quite similar to those experienced in the epilepsy trials, and are illustrated in Table 1.

The most common adverse events noted were hoarseness, dyspnea, and cough, and they appeared to be related to the intensity of the output current. Hoarseness, although it was a common adverse event, was generally experienced as mild in severity. Over the longer term, side effects appear to decrease, with only hoarseness during stimulation persisting as a fairly common event (27–54%). Also noteworthy is that vital signs and weight, when followed longitudinally, remain stable.

Psychiatric adverse events. *Hypomanic symptoms.* As might be expected with an antidepressant treatment, there have been some cases of treatment-emergent hypomania, but at a relatively low rate. In the open trial conducted by Sackeim, et al., 13 hypomanic symptoms occurred in two patients (3.3%). Hypomanic symptoms responded to a temporary reduction in intensity of VNS. In the larger randomized, controlled trial conducted by Rush, et al.,

three patients (1.2%) developed mild hypomanic symptoms, lasting only 1 to 3 days and subthreshold on DSM-IV criteria.[24] Two of the patients had a prior diagnosis of bipolar disorder and symptoms resolved spontaneously without treatment or change or adjustment in VNS stimulation.

Mania. In the same trial, three patients (1.2%) developed manic symptoms, meeting DSM-IV criteria.[24] In the first two cases, mania was mild, developing within three months of stimulation and subsiding within 1 to 2 weeks, without reduction or cessation of VNS. One patient had a history of bipolar disorder and the other had a history of treatment-induced mania. The third patient, with a previous diagnosis of major depression on study entry, developed a manic episode that lasted about two months and required hospitalization for stabilization. VNS was stopped until mania fully resolved but was ultimately re-started safely without further complications.

Exacerbation of depression and suicidality. In the trials conducted to date, albeit with small sample sizes, no evidence has emerged suggesting a potential for VNS to exacerbate depression or specifically induce suicidality. In the pivotal trial, exacerbation of suicidality was examined for on the suicide item of the 24-item HAM-D. Over the short term, in the 12-week sham/placebo controlled phase of the trial, the rate of treatment emergent suicidality, as defined by a two-point or greater increase in score on the suicide item from baseline, was three percent in the sham/placebo VNS group and two percent in the active VNS group.[25] Longer term, after one year of VNS, most patients (56%) had a reduction in score on the suicide item as compared to baseline. Another 34 percent experienced no change, leaving 10 percent with an increase of at least one point on the suicide item. Overall, the rate of treatment-emergent suicidality, as defined by a two-point increase, was three percent in the VNS group (5/181), which did not significantly differ from the two-percent rate (2/184) in the comparison TAU group of TRD patients without adjunctive VNS.[25]

Suicide attempts and suicide. The rate of suicide attempts in the combined VNS studies in TRD (n=345) was 3.5 percent per patient year. This rate can be compared to the rate reported by Khan, et al., in a review of nearly 20,000 patients participating in 45 studies of major depression with seven standard antidepressant medications (fluoxetine, sertraline, paroxetine, nefazodone, mirtazapine, bupropion, and venlafaxine). Khan, et al., found a suicide attempt rate of 2.9 percent on antidepressants and 2.7 percent on placebo in less severely ill depressed patients, suggesting absence of a suicide signal with VNS. Regarding completed suicides per patient year, the comparable rates are 0.4 percent for placebo, 0.8 percent for antidepressants, and 0.4 percent for VNS.[25]

Cognitive effects. VNS does not appear to have negative cognitive effects and may improve cognition in association with improvement in depression. Thus, Sackeim, et al., on administering a neuropsychological battery to TRD patients (n=27) before and after 10 weeks of VNS, found improvement in motor speed, psychomotor function, language, attention, memory, and executive functions.[26]

ADHERENCE AND VNS

Once implanted, the VNS device can remain functioning for up to eight years. Treatment delivery is automatic and assured and patients are unable to adjust the treatment settings independently. In the one-year pivotal study by Rush, et al., the continuation rate at one year was high at 90 percent. A small proportion (3%) discontinued secondary to adverse events, including implant-related infection, hoarseness, lightheadedness, postoperative pain, and chest and arm pain. The rest of patients discontinued because of lack of efficacy or other reasons. At two years, just over 80 percent of patients had device in place and functioning as reported by Nahas, et al., with most subjects electing to discontinue VNS because of lack of efficacy rather than side effects.[18]

After one year of VNS, most patients (56%) had a reduction in suicidality. Rates of treatment-emergent hypomania and mania were low (1–3%).

VNS IN THE CLINIC SETTING

Patient selection. VNS is intended for TRD patients with bipolar and unipolar depressive episodes as a long-term adjunctive treatment option. Clinicians may vary as to what point in sequential treatment failures that VNS will be considered, but at a minimum there must be four treatment failures over the lifetime course of depressive illness. It would be clinically prudent to require patient exposure to several classes of antidepressants, and in line with the entry criteria for the VNS trials, also insist on a trial of

psychotherapy. Failure to respond to ECT is not a prerequisite for VNS eligibility, and due to the different time courses of improvement with these neuromodulation modalities, it may on occasion be appropriate to use ECT as an acute treatment for severe depression to be followed by VNS as a long-term maintenance intervention.

Relative contraindications. VNS has not been approved for psychotic major depression or the depressed phase of schizoaffective disorder. In such situations, ECT will remain the treatment of choice in the setting of a TRD course. Similarly, the presence of paranoid ideation should be screened for as its presence would militate against the placement of an implanted device. Unstable axis II disorders, such as borderline personality disorder or other disorders, should be considered relative contraindications, as often the patient may lack sufficient stability to adhere with the demands of a surgical intervention with a slow trajectory of response. VNS has not been studied in pregnancy but as a non-systemic treatment its potential to have any direct effects on the fetus should be limited.

Special precautions with VNS. Due to the nature of the implant, patients need to be aware that MRIs of the spine or joints are prohibited. With special send-receive coils it is still possible to obtain an MRI of the brain, but otherwise a CT scan would need to substitute for an MRI. In the event of failure of an extended trial of VNS to be of therapeutic benefit, a patient may elect simply to have the device switched off and the implant left in place, or the patient can have the pulse generator explanted leaving the stimulus electrode *in situ*. The electrode is left *in situ* because of concerns that adhesions around the vagus nerve itself might increase risk of injury during removal of the electrode. Therefore, the precautions with MRI remain in place indefinitely. Other technology devices, such as cell phones, microwave ovens, or airport security systems should not have any adverse effects on functioning of the VNS device.

MRI of the neck or spine is contraindicated with VNS implant but MRI of the brain with a special send-receive coil is permissible.

Dosing VNS in the office. Programming visits to review VNS settings on the stimulator and monitor progress should take about 30 minutes. The patient holds a programming wand over the site of the implant and the psychiatrist communicates with the device by means of a handheld computer. The psychiatrist adjusts four principal settings: Current charge (in mA), pulse width (in microseconds), frequency (Hz), and on time relative to off time (in seconds, sometimes termed the duty cycle). Patients are generally started on stimulation at 0.25mA, and the current is increased gradually in 0.25mA increments until a comfortable tolerance level is reached. Full range of current dosing ranges from 0.25mA to 3.5mA, and the median dose in the 12-month pivotal trial was 1.0mA. The range of values for signal frequency is 1Hz to 30Hz, and a typical value is 20Hz. Pulse width can be varied from 130 microseconds to 1000 microseconds, and a typical value is 500 microseconds. The stimulus on time ranges from 7 seconds to 60 seconds with a typical value is 30 seconds. The off time can be set anywhere from 0.2 minutes to 180 minutes, and a typical value is five minutes.

Frequency of dosing visits. The first dosing visit is done about two weeks post surgery. It makes sense if possible to see the patient weekly for the first month to check tolerance and observe for mood changes carefully, as well as to allow 0.25mA titrations in current so that a target dose of 1.0mA might be achieved at the end of the first month. Visits can generally be conducted every two weeks in the second month. By three months, if the current amplitude is in the 1.0 to 1.5mA range and no improvement has been detected, most VNS clinicians would increase the duty cycle at the juncture by adjusting the on-off schedule. If improvement is on course, monthly visits should then suffice. Patients should be counseled that a significant proportion of responders to VNS only emerge in the second six months of stimulation and a full VNS trial may require at least 12 months.

Combining of VNS with existing treatments. One of the distinct advantages of VNS is that, due to its non-systemic nature, it can be combined with virtually all existing treatments for affective disorders. This is particularly helpful if response is slow or doubtful as the clinician is not precluded from consideration of other options. VNS has been combined safely with a wide range of medications, including MAOI antidepressants. Similarly, the VNS device can be temporarily shut off to permit ECT to be administered

and then restarted immediately post ECT.

SUMMARY

VNS is an important new addition to the armentarium of the clinician treating patients with severe unipolar and bipolar affective disorders. VNS appears to be a very safe form of treatment and the initial studies reviewed here do indicate that efficacy is promising, but given that there are some concerns still to be resolved regarding the full degree of treatment efficacy, close scrutiny should be applied to the post-FDA approval experience with VNS to get a fuller picture of its effectiveness in clinical practice. Unlike ECT, it does not cause adverse cognitive effects and is free of stigma in that regard, but its trajectory of therapeutic benefit is clearly slower than ECT. In that respect, these two neuromodulation modalities of treatment should be viewed as complementary, with ECT having the edge when rapid, robust improvement is required in the severely ill, and with VNS conferring the advantage of a very well tolerated long-term treatment with an important contribution to make in achieving and maintaining therapeutic response. Both devices, ECT and VNS, in turn are complementary to pharmacotherapy and psychotherapy of depression, and provide additional options for the large number of patients who, unfortunately, often fail to benefit from these first line approaches.

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. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 2001;16:10–7.
3. Trivedi M, Rush A, Wisniewski S, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006;163:28–40.
4. DeRubeis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. *Arch Gen Psychiatry* 2005;62:409–16.
5. Husain MM, Rush AJ, Fink M, et al. Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): A Consortium for Research in ECT (CORE) report. *J Clin Psychiatry* 2004;65:485–91.
6. Prudic J, Olfson M, Marcus SC, et al. Effectiveness of electroconvulsive therapy in community settings.[see comment]. *Biologic Psychiatry* 2004;55:301–12.
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, et al. A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. *Epilepsy Behav* 2000:93–9.
9. Elger G, Hoppe C, Falkai P, et al. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Res* 2000;42:203–10.
10. Krahl SE, Clark KB, Smith DC, Browning RA. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. *Epilepsia* 1998;39:709–14.
11. Ben-Menachem E, Hamberger A, Hedner T, et al. Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. *Epilepsy Res* 1995;20:221–7.
12. Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: A multicenter study.[see comment]. *Biologic Psychiatry* 2000;47:276–86.
13. 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.
14. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: A randomized, controlled acute phase trial. *Biologic Psychiatry* 2005;58:347–54.
15. Marangell LB, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. *Biologic Psychiatry* 2002;51:280–7.
16. Neurological Devices Panel of Medical Devices Advisory Committee FaDA. Report of 17th Meeting. 2004:1-433. Available at: www.fda.gov. Access date: December 1, 2005.
17. George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biologic Psychiatry* 2005;58:364–73.
18. 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.
19. Carlat D. Vagus nerve stimulation: Is the evidence convincing? *Carlat Report on Psychiatric Treatment* 2006;4:1–8.
20. Device Won Approval Though F.D.A. Staff Objected. *New York Times* February 16, 2006.
21. Maisel M. Medical device regulation: An introduction for the practicing physician. *Ann Intern Med* 2004;146:296–302.
22. Chai J. Medical device regulation in the United States and the European Union: A comparative study. *Food Drug Law J* 2005;55:57–80.
23. Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. *J Clin Neurophysiol* 2001;18:415–8.
24. Rush AJ, Sackeim HA, Marangell LB, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: A naturalistic study. *Biologic Psychiatry* 2005;58:355–63.
25. 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). Available at: www.fda.gov/ohrms/dockets/ac/04/briefing/4047b1_01_Clinical%20Executive%20Summary-FINAL.pdf. Access date: December 1, 2005.
26. Sackeim HA, Keilp JG, Rush AJ, et al. The effects of vagus nerve stimulation on cognitive performance in patients with treatment-resistant depression. *Neuropsychiatry Neuropsychol Behav Neurol* 2001;14:53–62.

VNS is an FDA-approved, well-tolerated, and safe long-term adjunctive treatment for depression. Efficacy is encouraging but more studies are needed to fully quantify it.