

ORIGINAL ARTICLE

Hamilton Rating Scale for Depression-21 Modifications in Patients With Vagal Nerve Stimulation for Treatment of Treatment-Resistant Depression: Series Report

Angelo Franzini, MD* • Giuseppe Messina, MD* • Carlo Marras, MD* • Mario Savino, MD[†] • Mario Miniati, MD[†] • Orso Bugiani, MD* • Giovanni Broggi, Professor*

*Fondazione Istituto Nazionale Neurologico, "Carlo Besta," Milan, Italy; and [†]Department of Psychiatry, University of Pisa, Pisa, Italy

ABSTRACT

Vagal nerve stimulation (VNS) has been approved for treatment of refractory depression (or treatment-resistant depression) and bipolar disorder in Europe and Canada since 2001 and in United States since 2004 by the Food and Drug Administration. Several lines of evidence support an effective antidepressant effect with such treatment modality, outcomes being mainly evaluated with Hamilton Rating Scale for Depression (HRSD). We here report a series of nine patients with severe treatment-resistant depression. They all underwent surgical intervention of implantation of left vagal nerve electrode at our institute. The preoperative psychiatric status and postoperative clinical outcome were both evaluated with the 21-item version of the HRSD (HRSD₂₁). Five out of nine patients, having at least one-year follow-up, were responders ($\geq 50\%$ reduction of HRSD scoring) and four of these also were remitters (HRSD < 10). One patient with bipolar II disorder and one patient with melancholic depression did not significantly benefit from the procedure; the latter three patients have follow-ups shorter than three months and one of them meets the remittance criteria; nonetheless, for the other two, HRSD₂₁ score is gradually decreasing with time.

KEY WORDS: *Vagal nerve stimulation, depression, Hamilton Rating Scale.*

Introduction

Depression is a disabling and often chronic psychiatric condition whose six-month prevalence is estimated to be about 5% for the general population (Depression Guideline Panel, 1993a). The depressive episodes tend to recur with time and to last longer than two years in about 10% of cases. Furthermore, 10–20% of depressed patients do not benefit from usual treatments as antidepressant medication, psychotherapy, light therapy, and electroconvulsive therapy (ECT). In some of these patients, vagal nerve stimulation (VNS) has proven to be an effective alternative

option in several studies recently published, and subjects who benefit from such treatment tend to maintain clinical improvement over time. Vagus nerve stimulation could exert antidepressant effect through the wide connections of vagus nerve with numerous brainstem and diencephalic structures, including nucleus tractus solitarius, nucleus parabrachialis, locus coeruleus, and several other nuclei harboring widespread projections to thalamic and cortical structures. Through these pathways, vagus nerve gains access to a variety of limbic subcircuits. Cortical limbic, paralimbic, and associative structures seem to be involved in such

Submitted: July 17, 2007; accepted: February 20, 2008. Address correspondence and reprint requests to: Giuseppe Messina, MD, Carlo Besta, Department of Neurosurgery, Via Celoria 11, Milan 20133, ITALY. Email: giumex@gmail.com

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mechanisms, as demonstrated by several functional magnetic resonance imaging, positron emission tomography (PET) and single photon emission computed tomography studies which revealed modification of brain metabolism in these regions following short- (1) and long-term (2) VNS treatment.

At present, many evaluation scales are employed for revealing clinical outcomes at follow-ups, Hamilton Rating Scale for Depression (HRSD) being the most popular and diffused. We here report a series of nine patients with long-lasting and disabling treatment-resistant depression (TRD) who underwent implantation of left vagal electrode for VNS and who underwent follow-ups at different time following surgery at our Institute, employing HRSD₂₁ as evaluation measure.

Materials and Methods

From January 2000 to November 2006, nine patients with TRD (age 43–80 years; five men and four women) came to our attention. Baseline scores were ≥ 20 on HDRS₂₁. For all of them, the current episode was lasting for at least two years; all of them had failed at least four antidepressant trials (Antidepressant Treatment History Form [ATHF] ≥ 3) in their current episode; such medical trials included serotonin reuptake inhibitors, noradrenaline reuptake inhibitors, monoamine oxidase inhibitors, tricyclics, benzodiazepines, and carbamazepine. All of them did not benefit from a minimum of six months of psychotherapy. Two patients (patients five and six) also underwent ECT with only transitorial benefit. None of these patients suffered from atypical depression, depression with psychotic features, or schizoaffective disorder.

They then underwent presurgical psychiatric evaluation at our Institute. It was performed by our reference psychiatrist (M.S.), and confirmed the great degree of resistance of such patients and the absence of generic medical conditions which could contraindicate the surgical intervention.

They were then admitted at our Institute for VNS. Before intervention, all patients underwent HRSD₂₁ testing, further psychiatric and neuropsychological evaluation, mini-mental state examination, brain PET scan and dynamic electroencephalogram monitoring. Such examinations have been employed to rule out comorbidity for other neurologic diseases which may be associated or be at the origin of major depression, for example, extrapyramidal disorders (Parkinson's disease, progressive supranuclear palsy, multisystem atrophy), ischemic lesions, or dementia. After intervention all patients were submitted to weekly (for the first month) psychiatric evaluation and HRSD, and then followed monthly. Stimulation parameters were 30 Hz, 500 μ sec, 30 sec on and 5 min off cycle for all patients. All patients (except for patients five and six, who received 1.75 mA current intensity) were stimulated with 1.5 mA. During follow-up evaluations, stimulation parameters also were adjusted and any adverse effect documented.

Surgical Procedure

All of the patients underwent the standard surgical procedure of implantation of the left vagal stimulation system. After general anesthesia, a transverse skin crease incision was made on the left side of the neck at the level of the fifth or sixth cervical vertebra. After dissection of subcutaneous tissue and division of the platysma muscle, the middle cervical fascia and the anterior border of the sternocleidomastoid muscle were exposed. After retracting such muscle, the carotid sheath was sharply opened, disclosing carotid artery medially, and jugular vein laterally. Through sharp dissection, the left vagus nerve was so found laying deep to and between these two vessels and the coil-shaped vagal electrode and then positioned. The distal wire of the electrode was then connected to the pulse generator (located in a subcutaneous pocket in the left anterior axillary fold) through subcutaneous tunneling. The surgical wounds were closed in the usual fashion.

Immediate Postoperative Period

No major adverse event, including infection or arrhythmia, occurred either during the intervention or in the postoperative period. Few days after surgery, the pulse generators were activated and the initial stimulation parameters were set according to the Manufacturer's indications (Cyberonics Inc., Houston, TX, USA): 0.25 mA, 30 Hz, 500 μ sec, 30 sec on, 5 min off. None of the patients met the response criteria ($\geq 50\%$ reduction of HRSD₂₁ scoring) in the first week postimplantation period, which could be strongly suggestive of a placebo effect.

Outcome

PET scans disclosed bilateral temporal gyri, bilateral parietotemporal and bilateral frontal hypometabolism in three patients (patients three, five, and six), respectively. Dynamic electroencephalogram disclosed absence of deep sleep stage 4 in all but one patient (patient one). Neuropsychological examinations revealed, in two patients (patients three and six), mild deficits of planning functions and of comprehension of mental status. MMSE anyway disclosed a normal score for all patients (comprising patient one, whose clinical features could initially lead to a diagnosis of dementia) taking into account the age and the educational level (Table 1). After implantation, hoarseness was the only adverse effect observed; it was initially present in all patients after titrating intensity of current (IC) up to 0.5 mA but gradually decreased with time in all of them.

The only clinical postoperative evaluation scale we used was the HRSD₂₁ scoring.

Patient One

A 70-year-old woman came to our attention in 2000. For five years, she had been suffering from severe treatment-resistant major unipolar depression, with clinical picture

TABLE 1. Preoperative MMSE Scores for the Nine Patients; They All Resulted Normal Taking into Account Age and Educational Level (3)

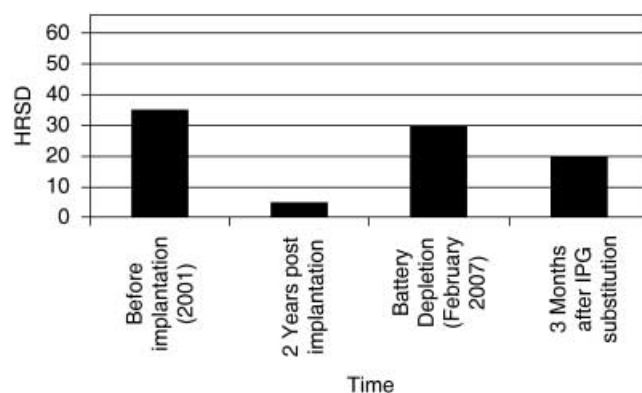
Patient no.	MMSE score
1	26
2	28
3	22
4	29
5	29
6	30
7	30
8	28
9	28

MMSE, mini-mental state examination.

dominated by frequent motor immobility, motiveless resistance to all instructions, behavioral mannerism and, sometimes, echolalia and echopraxia. The patient did not present symptoms, such as hallucinations, delusions, or psychomotor agitation; the psychiatric evaluation did not consider such symptoms as being mood-incongruent and the final diagnosis was of major unipolar depression with catatonic features (according to *DSM IV-TR*). Her presurgical HRSD₂₁ score was 44. VNS treatment had still not been approved in Europe for treatment of TRD, so she underwent compassionate treatment. After few months after beginning of VNS, she started to improve, with restoration of motor functionality, speech, and interest in daily activities. Her HRSD₂₁ score at a follow-up in 2004 was 20 (responder); she underwent battery substitution on 2005 and the benefit was confirmed by a further visit on January 2007 (HRSD₂₁ 19).

Patient Two

A 65-year-old woman was operated on in 2001. She had been suffering from severe-resistant major unipolar depression with melancholic features (loss of pleasure in all activities, depression worse in the morning, psychomotor retardation, early morning awakening, *DSM-IV-TR*) for 10 years. Her preoperative HRSD₂₁ score was 35. At 1- and 2-year postimplantation follow-ups, she had completely recovered in all aspects of daily living and the HRSD₂₁ score was 5 (remitter).

**FIGURE 1.** HRSD₂₁ modification in patient two. Note the increase of HRSD₂₁ during the period of exhausted pulse generator and its decrease after replacement.

Anyway, on February 2007, she started complaining of gradual recurrence of her depressive symptoms; HRSD₂₁ score at that time was 30. VNS pulse generator control revealed battery depletion; after internal pulse generator substitution, she is starting to improve and her last postoperative follow-up (three months) revealed a HRSD₂₁ score of 20 (Fig. 1).

Patient Three

An 80-year-old woman came to our attention because of melancholic TRD (lasting five years) accompanied by somatic symptoms (sensation of “burning” and “flushing” at the right hemiface and in the right eye) occurring during the “saddest” moments of day, mainly in the morning. The preoperative HRSD₂₁ score was 27. She underwent implantation on January 2006. At one-year follow-up examination, such score has decreased to 9 (remitter) and she no longer has somatic complaints.

Patient Four

A 43-year-old man, suffering from TRD (lasting 18 years) with severe anxiety comorbidity and social phobia, was operated on January 2006. His preoperative HRSD₂₁ score was 25. At one-year follow-up, this score has decreased to

TABLE 2. Preoperative Medication Regimen of the Nine Patients Submitted to Vagal Nerve Stimulation

Patient no.	Daily medication regimen
1	Venlafaxine 75 mg; trimipramine 250 mg
2	Clomipramine 75 mg; lorazepam 1 mg
3	Venlafaxine 75 mg; bromazepam 15 gtt; paroxetine 20 mg; trimipramine 100 mg; carbamazepine 600 mg
4	Clomipramine 150 mg; lorazepam 2 mg
5	Mirtazapine 30 mg; amisulpride 100 mg; seleginine 20 mg; lithium carbonate 600 mg
6	Clomipramine 75 mg; lorazepam 1 mg
7	Tranlycypromine 10 mg; trifluoperazine 1 mg; lorazepam 2.5 mg
8	Clomipramine 150 mg; paroxetine 20 mg
9	Venlafaxine 300 mg; mirtazapine 30 mg

8 (remitter) and he also refers improvement of anxious symptoms and disappearance of social phobia.

Patient Five

A 51-year-old man came to our attention because of bipolar II disorder, with major depressive episode being the most recent and invalidating. He had not been suffering from hypomanic symptoms for about two years and a half before admission. His mood disorder had been lasting for 23 years. He was operated on March 2006. Preoperative HRSD₂₁ score was 24. At three-month follow-up, this had decreased to 11. The psychiatric examination also disclosed recurrence of hypomanic episodes. At six months, he started to worsen, complaining of recurrence of severe depressive symptoms, mainly loss of pleasure in all activity, including work, and sad mood for most of the day. He then underwent several medical antidepressant treatment adjustments, although without benefit over time. At one-year follow-up, his HRSD₂₁ score is 25 (nonresponder) and hypomanic symptoms no longer persist.

Patient Six

A 66-year-old man, suffered from unipolar melancholic major depression, also with catatonic features, for five years, was operated on April 2006, preoperative HRSD₂₁ score being 28. At one-year follow-up, the score is still high (24: nonresponder) and none of his depressive symptoms seems to have significantly improved with time. Nonetheless, because current intensity was titrated from 1.5 mA (which he had maintained for most of the postoperative period) to 1.75 mA, melancholic and catatonic features are slightly improving, as disclosed by a recent telephone interview. Further follow-ups for this patient are then necessary for complete evaluation of outcome.

Patients Seven, Eight, and Nine

Do not have long-term follow-ups (the first two were operated on February and the third on March 2007). Patient seven was a 40-year-old man, patient eight was a 55-year-old woman, and patient nine was a 43-year-old man. All of them suffered from melancholic unipolar major depression for a minimum of five years. Preoperative HRSD₂₁ scores were 33, 25, and 30, respectively. At two-month follow-up, such scores decreased to 22, 21, and 26. Patient seven, anyway, does have four-month follow-up, and the control visit revealed a HRSD₂₁ of 9 (remitter). In the two months between the last two visits, they did not undergo pharmacologic therapy augmentation or medication changes.

Discussion

The most widely employed evaluation scale in all previous reports on VNS and depression for monitoring of short- and long-term outcome results to be the HRSD, maybe because of its intuitiveness and ease of use.

Although our present series only includes nine patients, the preliminary follow-up results observed seem to confirm what has been reported in the previous studies. The percentages of responders (five out of nine; 55%) and remitters (four out of nine; 44%), as determined using HRSD₂₁, are in line with larger previous prospective multicenter studies. Rush et al. (4) reported percentages of responders and of remitters of 40% and 17%, respectively, at a 12-week acute study exit. At one-year study extension, an increase in both percentages (44.1% and 27.1%, respectively) was observed (5), and two-year outcome disclosed sustained benefit (42.4% and 22%) (6). Even these studies, of course, included patients with nonpsychotic, treatment-resistant major depressive or bipolar I disorders.

George et al. reported that VNS together with usual antidepressant treatments was associated with a greater antidepressant benefit, if compared with usual antidepressant treatments alone, over a period of 12 months (7). It remains unclear, though, whether VNS exerts an antidepressant effect by itself or if it makes antidepressant drugs more effective, and such issue should be object of further and dedicated studies.

In our series, responders kept medication regimen stable with time (Table 2), whereas patients who were nonresponders (patients five and six) at one-year follow-up underwent medication's augmentation and shifting (patient five switched to a daily dosage of perphenazine 2 mg + amitriptyline 25 mg and patient six underwent medication augmentation with 150 mg of clomipramine instead of 75 mg) and benefited from ECT only for a short-time period. This also seems to agree with the report of Sackeim et al. (8), who found a significant relationship between ATHF scores/response to ECT and clinical outcome evaluated with HRSD.

We think that undoubtedly there is still much more to know about the physiopathologic characteristics of depressive disorders and about its heterogeneity, in order to address what patients are more likely to benefit from VNS. More detailed and dedicated functional neuroimaging studies, such as functional magnetic resonance imaging, brain PET and single photon emission computed tomography, and a better knowledge of the genetic of depressive disorder will certainly contribute to answer this question.

In our series, the time lapse between surgery, activation of the stimulation, and the therapeutic effect ranges between three and six months, while a placebo effect should be expected after a shorter time interval; for such reason, we think that a placebo effect was unlikely in our series, also taking into account the high treatment resistance of our patients and the sustained benefit that responders obtained over time.

In conclusion, with HRSD₂₁ seriate evaluations, we could monitor patients' psychiatric status in a simple and straightforward fashion, and in all cases it was in line with close relatives' reports and impressions. In other words,

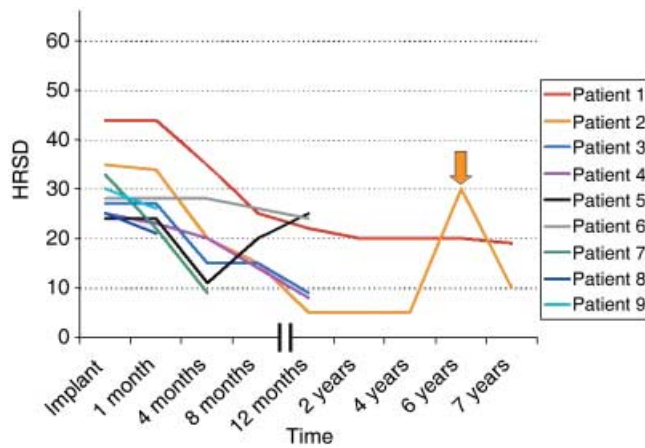


FIGURE 2. Overall of HRSD₂₁ modifications in the whole series. Patients are numbered as in the text and coded by different colors. Note the profiles of the two nonresponders patients (patients five and six). The arrow points to the HRSD₂₁ score at the moment of battery replacement.

HRSD may be used in depression as the visual analog scale is used in pain to evaluate the response to neuromodulation procedure. Despite the small number of patients operated on, this report suggests that HRSD₂₁ rating scale results to be a valid mean of assessment of clinical outcome in patients submitted to vagal electrode placement for refractory depression (Fig. 2). Further evaluation with a larger number of patients is, of course, necessary to confirm our preliminary

results suggesting the antidepressant effect of VNS beyond the placebo effect.

Conflict of Interest

The authors reported no conflict of interest.

References

1. Lomarev M, Denslow S, Nahas Z, Chae JH, George MS, Bohning DE. Vagus nerve stimulation synchronized BOLD fMRI suggests that VNS in depressed adults has frequency and/or dose dependent effects. *J Psychiatr Res* 2002;36:219–227.
2. Conway CR, Chibnall JT, Li X, George MS. Changes in brain metabolism in response to chronic vagus nerve stimulation in depression. *Biol Psychiatry* 2002;51:8S.
3. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA* 1993;269:2386–2391.
4. Rush AJ, George MS, Sackeim HA et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: a multicenter study. *Biol Psychiatry* 2000;47:276–286.
5. Marangell LB, Rush AJ, George MS et al. Vagus nerve stimulation (VNS) for major depressive episodes: one-year outcomes. *Biol Psychiatry* 2002;51:280–287.
6. 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;25:713–728.
7. George MS, Rush AJ, Marangell LB. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry* 2005;58:364–373.
8. 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;66:1097–1104.