

# Ten-year outcome of vagus nerve stimulation-implanted patients with treatment-resistant depression: two Italian cases

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**Abstract:** Over the last 15 years, vagus nerve stimulation (VNS) has been used as an augmentative therapeutic intervention in patients with treatment-resistant depression (TRD), whether with a lifetime diagnosis of major depressive disorder or bipolar disorder. From being a potentially effective treatment in the acute phase of TRD, recently published treatment guidelines seemed to converge on the indication that VNS's greatest benefit may be seen mostly beyond the short term. However, with the exception of a recent multicenter American report, very few studies have assessed the long-term efficacy of VNS in TRD patients. Herein, we present the cases of two Italian patients with TRD, with 10-year VNS follow-up evaluation. Both patients were found to benefit from augmentative VNS, and the latency of their stimulation response, tolerability, associated pharmacological treatment, number and duration of recurrences, and overall level of functioning are described and discussed. Further reports with larger samples are needed to support the long-term efficacy and tolerability of VNS in TRD patients, particularly beyond 5 years of follow-up.

**Keywords:** vagus nerve stimulation, treatment-resistant depression, long-term follow-up, MDD, bipolar disorder

## Introduction

Vagus nerve stimulation (VNS) is a brain stimulation technique originally approved in 1997 for drug-resistant epilepsy by the US Food and Drug Administration (FDA) and, between 2001 and 2005, extended to treatment-resistant depression (TRD) by FDA and European Medicines Agency (EMA).<sup>1</sup> VNS implant consists of an extracranial surgical intervention with an electrode wrapped around the vagus nerve and connected to a pulse generator placed subcutaneously in the chest area.<sup>2</sup> Such a procedure is nonablative, reversible, and adjustable.<sup>3</sup>

Currently, VNS represents an effective nonpharmacological augmentative therapeutic intervention for patients with TRD, and it has been approved for such an indication by the EMA in 2001 and by the FDA in 2005.<sup>4</sup>

Despite the lack of an overall consensus on the definition of TRD, this condition has been previously outlined as the absence of response to at least two antidepressant trials, given in succession, at adequate doses and for an adequate time, in compliant subjects.<sup>5,6</sup> TRD is prevalent in ~30% of patients affected by major depressive disorder (MDD).<sup>7,8</sup> A formal definition of treatment-resistant bipolar disorder (TRBD) as a complete entity still needs to be formulated, and it does not seem to be a simple sequence of treatment-resistant depressive and hypomanic/manic episodes.<sup>9</sup> A number of different parameters

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have been suggested as characteristic criteria for TRBD, such as the specific disorder phase, the number of previous unsuccessful treatments, and the definition of response.<sup>10</sup> Notwithstanding, TRD in bipolar disorder (BD) has been defined as the failure to obtain a therapeutic response after adequate treatment with lithium or mood stabilizer plus lamotrigine or quetiapine, within a specified dose range.<sup>11</sup>

Focusing on VNS in TRD, most recent international guidelines for the treatment of MDD, particularly the CANMAT 2016 and WFSBP 2015, indicate VNS long-term results as promising and suggest that the greatest antidepressant effect of VNS may occur over time.<sup>4,12</sup> With regard to TRBD, a few long-term open studies reported the antidepressant property of VNS, suggesting similar short- and long-term results (up to 2 years) in comparison to unipolar patients.<sup>13–15</sup> To the best of our knowledge, long-term studies with VNS in TRD patients are limited, and the follow-up extent of available reports in the field is limited to 5–6 years.<sup>16–18</sup> In order to provide further evidence about the long-term efficacy and tolerability of VNS in TRD, the present report describes the 10-year follow-up results of two Italian patients with TRD implanted with VNS. Both patients were suffering from TRD, with a lifetime diagnosis of bipolar depression (Patient 1) and MDD (Patient 2), respectively.

The study was conducted in accordance with ethical standards (eg, written informed consent form was obtained). Additionally, patients signed an informed consent to acknowledge the publication of their clinical data. The stimulation parameters, the inclusion/exclusion criteria, and the assessment procedure for the study are described elsewhere.<sup>19</sup> Standard definitions of response and remission were adopted. Recorded clinical variables consisted of number, severity, and duration of depressive recurrences (from 12 months preimplant to the following 10 years) and spontaneously reported side effects. Standard psychometric scales were used as outcome measures: Hamilton Depression Rating Scale 21-items (HDRS<sub>21</sub>), Montgomery–Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HARS), Sheehan Disability Scale (SDS), and Clinical Global Impressions Item Severity (CGI-S) and were used at baseline and 10-year mark.

Previously, we reported results at 1 and 5 years of follow-up for TRD patients treated with VNS. The original sample consisted of six patients with a diagnosis of treatment-resistant MDD (n=1) or TRBD (n=5), of whom two had rapid cycling features. The clinical and sociodemographic variables as well as the stimulation parameters are published elsewhere. The present report describes the outcome of the only two patients who recently completed the 10-year follow-up.<sup>13,19</sup>

## Patient 1

Patient 1 is a 70-year-old Caucasian woman whose psychopathological onset dated to her adolescence. In fact, she experienced her first depressive episode at 17 years of age and underwent her first psychopharmacological treatment at 18. From then on for the subsequent 40 years, she experienced several depressive, mixed, and hypomanic episodes. She has visited many specialists (neurologists and psychiatrists) and had been treated with several psychotropic compounds belonging to different classes including antidepressants (tricyclics, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors), antipsychotics (first and second generation), and mood stabilizers. Electroconvulsive therapy had been offered to the patient before she came to us, yet she had refused such therapy repeatedly.

Patient 1 came to our attention in March 2005, at the age of 58. The diagnosis of BD type 2 was formulated, according to the structured clinical interview for *DSM-IV-TR* axis I disorders (SCID-1). Within the clinical picture, in fact, the presence of mixed-depressive episodes, characterized by dysphoria alternating with depressed mood, irritability, decreased energy, hypersomnia, and mild levels of anxiety, was highly prevalent.

Patient 1 used to experience about five episodes per year (both mixed and depressive), showing therefore features of rapid cycling BD. On average, one episode lasted about 21 days, and the depressive symptoms, recorded by means of the abovementioned psychometric scales, showed moderate severity, as evidenced by the scores on the HDRS<sub>21</sub>, 18; MADRS, 22; HARS, 9; and CGI-S, 4 scales. Her quality of life, evaluated through the SDS, was considered poor (22).

Patient 1 first underwent a 3-week (five applications per week, 15 in total) low-frequency repeated transcranial magnetic stimulation (rTMS) (targeting the right dorsolateral prefrontal cortex),<sup>20</sup> with only limited benefit, in terms of effect duration (<6 months). She was then considered a potential candidate for VNS, and the device was implanted in November 2007. The therapy at the time of implant consisted of bupropion 150 mg per day, valproate 250 mg per day, and pramipexole 0.7 mg per day. The optimal stimulation current output of 1.5 mA was reached within 3 months from implant. After 3 months, due to the persistence of such side effects as hypophonia, hoarseness, and cough, the pulse width was adjusted from 500 to 250  $\mu$ s, and the current output was decreased to 1.25 mA, resulting in an overall better tolerability.

After the implant, the clinical picture gradually changed. The patient experienced, on average, 1.5 episodes per year (overall reduction: 80%). In addition, each episode lasted ~8 days (overall reduction: 62%) and showed a decreased severity in comparison to the preimplant period.

In particular, at 10 years from the implant, the psychometric total scores were as follows: HDRS<sub>21</sub>, 4; MADRS, 6; HARS, 4 (reduction: included between 56% and 73%); and CGI-S, 2 (50% improvement). The quality of life increased and remained at a satisfying level (SDS 6, 73% improvement). As a housewife, Patient 1 now manages to look after the house and her grandchildren, unlike before the VNS implant.

A change of battery was necessary 6 years from the implant. In that circumstance, the generator model was changed as well (from model 102 to 103). Such procedure did not cause any adverse event. No relevant changes in the clinical course were observed. The original pharmacotherapy was gradually changed due to the achievement of clinically stable condition and, at the 10-year follow-up, consists of only *s*-adenosyl methionine, 400 mg per day.

## Patient 2

Patient 2 is a 47-year-old Caucasian patient who experienced his first depressive episode in 2003, at the age of 33. For that reason, the patient was hospitalized and treated with pharmacological therapy (one selective serotonin reuptake inhibitor and one atypical antipsychotic). He was admitted to the hospital twice in the first year after his psychopathological onset, due to the persistence of depressive symptomatology. In the following years, the patient changed a number of psychiatrists and therapies, including antidepressants (tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors), atypical antipsychotics, and mood stabilizers. In terms of medical history, the patient was diagnosed with Behçet's disease in 2000, at the age of 30. In 2004 and 2005, he was admitted to hospital as a result of an ischemic stroke. Due to such events, conditioned by a peripheral neuropathy, he was treated with gabapentin up to 900 mg per day. In January 2007, Patient 2 attempted suicide, ingesting about 4 g of gabapentin. Electroconvulsive therapy was not considered a feasible option for this patient, due to the increased safety risk owing to his ischemic stroke history.<sup>4</sup>

Patient 2 came to the outpatient unit of our clinic in August 2007, at the age of 37, while experiencing a severe depressive episode, which was lasting >3 months. When administered, the SCID-I showed a lifetime diagnosis of MDD. The clinical picture was characterized by anhedonia, hopelessness, low self-esteem, lack of motivation and energy, loss of libido, disturbed sleep with excessive time spent in bed during day, and moderate anxiety. He lived with his parents, had not been working in the previous year, and had no partner in the previous 3 years.

Patient 2 used to experience ~1.5 episodes per year, with an average duration each of ~4 weeks per episode. The

severity of the depressive picture was considerable and, when the abovementioned scales were administered at the baseline, they showed the following scores: HDRS<sub>21</sub>, 25; MADRS, 27; HARS, 21; CGI-S, 5; and SDS, 25.

A preliminary 3-week (five applications per week, 15 in total) high-frequency rTMS (targeting the left dorsolateral prefrontal cortex) had been previously administered.<sup>20</sup> In November 2007, he was implanted with the VNS device. The therapy at the time of implant consisted of mirtazapine 30 mg per day.

The current output of 1 mA was reached in ~3 months, with gradual increases of +0.25 mA per week. Due to the resolution of the ongoing MDD, the stimulus intensity was not additionally increased. The only side effect reported was hypophonia, in line with the literature data and described as tolerable by the patient. No pulse width adjustment was required.

The clinical picture of Patient 2 significantly changed after VNS implant. He experienced one brief depressive episode in the first year after VNS implant (lasting ~1 week), and then no further depressive episode was reported. The psychometric scales, administered at regular intervals, returned almost null values. The CGI-S at 10 years from implant showed a score of 1. The patient gradually resumed his social life, got married in 2009, and had two children (2010 and 2015). In addition, he restarted working in a full-time job (a family-owned bakery shop). At 10 years, the SDS score was 0 (100% improvement).

A change of battery and pulse generator (from model 102 to model 103) became necessary at 6 years from the implant, without any adverse event. The clinical picture showed a stable course over the subsequent years, and therefore the initial pharmacotherapy was gradually suspended. At 10 years from the implant, Patient 2 is drug free.

## Discussion

The described cases of VNS-implanted patients support the guidelines that such brain stimulation techniques may effectively exert a long-term (up to 10 years) antidepressant action, with limited and tolerable side effects. No manic episodes were observed over the 10 years course, although such an adverse event has been previously documented.<sup>21</sup> Of note, after the implant, pharmacological treatment was gradually decreased, both in terms of number of medications and dosage, while both patients remained clinically stable.

The latter results, despite the limited sample size, support the evidence that VNS might produce a persistent and long-term benefit, reducing not only the number of depressive recurrences but also the duration and the severity of each

affective episode, therefore ameliorating the overall quality of life. As a matter of fact, we took into account the fact that both patients managed to resume their usual occupation and a satisfying relationship with their family.

Moreover, with respect to the case of Patient 1, VNS showed a positive action specifically over the cyclicity of BD. These results support the hypothesis that VNS may have stabilizing properties that manifest beyond the acute phase, reducing the cyclicity that characterizes many difficult-to-treat phenotypes of mood disorders.<sup>14,22</sup> Affected patients, in fact, often present a higher index of recurrence, a higher rate of physical and mental comorbidity, and struggle to reach the most important life milestones. It is finally important to highlight that both patients had previously received an acute course of TMS with poor benefit, particularly in the long term.

It is worth highlighting as a limitation that the present case report describes two patients who recently completed a 10-year follow-up; thus, the latter results have a descriptive intent. Larger controlled trials need to be conducted to further investigate these patients, with the aim to test their acute and long-term response to VNS.

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## Disclosure

The authors report no conflicts of interest in this work.

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