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Sustained remission in patients with treatment-resistant depression receiving vagal nerve stimulation: A case series

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Dear Editor,

One third of patients suffering from major depression fail to respond to available standard treatments [1] and are considered treatment-resistant major depression (TRMD). TRMD is associated with reduced quality of life, disability, high rates of co-morbid illnesses, and substantially increased resource utilization [2]. Left cervical vagus nerve stimulation (VNS) via an implantable electrical pulse generator is a well-tolerated, FDA-approved treatment for TRMD. Although a subset of patients experience relatively rapid antidepressant response to VNS (within 1–2 months), most TRMD patients experience antidepressant benefit only after many months of stimulation (6–24 months) [3,4].

A critical challenge in the management of TRMD patients is to sustain antidepressant remission and minimize relapse. Results from the largest clinical depression trial to date, the Sequenced Treatment Alternatives to Relieve Depression or STAR*D, demonstrated that the likelihood of both remitting and maintaining remission for one year in patients at levels 3 and 4 of the trial was disappointingly low (5% and 3% respectively [5]).

Existing data on the antidepressant effect of VNS supports that those responding to VNS maintain the response at one and two years [3,4]. A recently published observational study compared antidepressant outcomes in 795 patients with TRMD, including 494 patients receiving VNS for 60 months [6]. This study demonstrated a 5-year cumulative remission rate of 43.3% with VNS (vis-à-vis 25.7% in the treatment-as-usual group). Now that the FDA approval of VNS for TRMD is greater than a decade old (2005), we can begin to assess if VNS can sustain antidepressant effects beyond 5 years.

We currently report a series of six TRMD patients with well-characterized pre-treatment histories of TRMD, who, following VNS implantation, experienced an average of over nine years of sustained antidepressant remission.

Methods

We recruited six subjects with DSM IV-diagnosed major depressive disorder and documented histories of TRMD, who have been receiving VNS with regular follow-up at Washington University. These subjects have previously participated in prospective studies conducted at Washington University and St. Louis University as part of multicenter VNS TRMD trials [6–8]. The study was approved by the Washington University Institutional Review Board, and all patients provided written informed consent.

Data were extracted from chart review, archived data from the original studies, and a one-time in-person interview (last reported data) during which a battery of assessments and rating scales were performed including the Montgomery-Åsberg Depression Scale (MADRS, reported here) and a customized illness burden questionnaire. Analyses were limited to descriptive statistics, means and standard deviations.

Results

All subjects (four males, two females, mean age 60.3) were Caucasian, highly educated (mean: 4.2 years post secondary), with a primary diagnosis of MDD, mean age of onset of 29.3 and mean pre-implantation duration of illness of 20.5 years. On average, the sample had 0.8 previous psychiatric hospitalizations and 8.5 documented failed, adequate dose-duration antidepressant trials (50% failed electroconvulsive therapy [ECT] and 50% failed monoamine oxidase inhibitor [MAO-I] treatment). Psychiatric comorbidities were rare: one subject had alcohol use disorder (in remission) and another had an unspecified anxiety disorder. Of note, there was a strong family history of alcohol dependence (100% of the sample had a first-degree relative with alcohol dependence) and mood disorders (80% of the sample had a first-degree relative with a mood disorder).

Table 1 presents the clinical course and characteristics of each subject; Fig. 1 graphically depicts depression symptomology (MADRS) scores at various time points. VNS electrical settings were as follows (Mean ± SD): Output current = 0.83 ± 0.4 mA, signal frequency = 20 ± 0 Hz, and pulse width = 293 ± 169 μs.

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Table 1
Clinical course and characteristics by subject.

Subject	Age	Gender	Pre-VNS Duration of Illness (years)	Longest Remission pre-VNS (years)	MDE pre-VNS (years)	Total time in remission post-VNS (years)	Post-VNS course
A	63	Male	33	0.5	5	6	Subject remitted at 6 months and has been in full remission since. He started his own business and makes regular missionary trips to Africa.
B	66	Male	19	2.5	8	6.3	Subject remitted at 3 months and sustained remission for 3 years. In post-implantation year 3, he was diagnosed with prostate CA with re-emergence of depressive symptoms. His MDD symptoms resolved spontaneously after successful cancer treatment. He then regained full remission status for the following two years (until present), without adjunctive pharmacotherapy.
C	54	Male	15	0.5	0.4	6.5	Subject responded at 3 months followed by remission at 6 months. 3 years later, he relapsed after a VNS battery failure, which was replaced at month 44. He returned to remission 10 months later; has been in full remission for 6.5 years.
D	54	Female	21	0.75	0.5	8.3	Subject had a rapid remission within 3 months and remained in remission for the following 8 years. She currently is on one antidepressant medication-down from four different pre-VNS psychotropics.
E	57	Male	16	0.25	2.4	14	Subject gradually improved after 9 months of VNS; remission achieved at 12 months. He relapsed after 3.8 years, following a device lead break [10] not depicted in figure, as MADRS scoring was not taken during this interval. At 2 weeks post-surgical device replacement, he again achieved and has since sustained remission.
F	68	Female	19	0.25	1.2	14.3	Subject remitted at 3 months followed by a short relapse at 7 months and back into remission at 9 months. She has now been in full remission for more than 14 years.

The mean total time in remission post-VNS was 9.2 years with no reported suicidal ideation or attempts, and no post-implantation psychiatric hospitalizations, except one subject admitted overnight for severe anxiety after mirtazapine initiation (spontaneously resolved).

Discussion

To our knowledge, this is the first description of chronic and sustained antidepressant effects of VNS for TRMD beyond five years duration. The TRMD subjects in this case series experienced nearly a decade of full remission after VNS implantation, with some being symptom-free for more than 14 years.

Several noteworthy observations emerge from these cases. First, all had a well-documented history of severe TRMD prior to VNS, with an average of more than twenty years of chronic symptoms, very short inter-episodic remissions, and multiple failed treatment trials. These sustained VNS-associated responses are quite unusual among TRMD patients, as STAR*D found that antidepressant resistance was associated with a very high rate of relapse following responses to treatments [5]. This persistent antidepressant efficacy may suggest that VNS is acting via different pathways than antidepressant medications. Second, the subjects have heavy family histories of depressive illness and alcoholism. The latter finding is particularly interesting as family history of alcohol use disorder has been previously associated with antidepressant response to ketamine in TRMD [9]. Third, VNS antidepressant efficacy appears to be resilient: in three of the six cases (B, C, and E in Table and Fig. 1) device-related interruption of stimulation (C and E) or major medical illness (prostate cancer with chemotherapy) led to re-emergence of depression. Once repaired/restored to health, all three patients regained full remission. One of these cases (E) has been previously described [10].

There are several limitations to this case series. We acknowledge the selection bias in this sample, i.e., we knowingly selected TRMD patients who had sustained VNS antidepressant response. We do not intend to suggest that all TRMD patients will have a similar response, but rather, to demonstrate that a subset of patients, with histories of well-characterized, severe, and prolonged TRMD can achieve protracted antidepressant remission with VNS. Additionally, the absence of formalized rating scales performed beyond the period of the clinical trials in which the subjects were enrolled poses another limitation. However, we did access regular clinic notes and interviews, as well as patient recall, to retrace the subjects' illness trajectory to date.

In summary, this case series demonstrates a persistent and potentially “near permanent” antidepressant response to VNS in the treatment and maintenance of at least some patients with severe TRMD.

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