Vagus Nerve Stimulation

Changing the Paradigm for Chronic Severe Depression?

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KEYWORDS

• Major depression • Treatment-resistant major depression • Vagus nerve stimulation • Neurostimulation

KEY POINTS

- Treatment-resistant depression (TRD) affects at least a third of patients with depression and there is scant evidence to guide treatment of those who have failed four or more trials of somatic therapies.
- Vagus nerve stimulation (VNS) was cleared in 2005 by the Food and Drug Administration (FDA) for use in TRD after patients had failed at least four antidepressant trials on the basis of two large clinical trials, although a noncoverage determination (NCD) issued in 2007 by the Centers for Medicare and Medicaid Services has dramatically limited its availability.
- Two large randomized studies failed to reach their primary outcome measure, likely in part because of the 6 to 9 months it takes to achieve response after the device is turned on and because of low, chronic stimulation providing some positive effect.
- A recent open-label, naturalistic study of 795 TRD patients (494 patients receiving VNS and 301 patients receiving treatment as usual) followed over 5 years showed a much great likelihood of achieving response and remission if implanted with VNS.

Epidemiologic evidence suggests that the incidence of major depressive disorder (MDD) is growing with a lifetime prevalence of almost 30% and a yearly prevalence of 9%.[1] Antidepressant medications, the mainstay of somatic therapy for depression, show only a mild to moderate effect size (0.20–0.40) for acute antidepressant response.[2]

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Serial antidepressant treatment trials demonstrate that more than 60% of depressed patients fail to remit after an initial pharmacotherapy trial, and progressively fewer remit with subsequent trials until the fourth antidepressant trial yields a remission rate of 10% to 14%.[3–5] Treatment-resistant depression (TRD) refers to major depression that fails to remit after two antidepressant treatment trials of adequate dose and duration. The Sequenced Treatment Alternatives to Relieve Depression trial (STAR*D) demonstrated that 32% to 41% of depressed patients fail to achieve antidepressant remission after four antidepressant trials, resulting in a large population of symptomatically and functionally impaired individuals with clear TRD.[4] There is scant evidence to guide treatment of TRD patients who have failed more than four trials of somatic therapies.

In 2005, the Food and Drug Administration (FDA) approved vagus nerve stimulation (VNS) for the treatment of MDD (unipolar and bipolar) after failure of at least four adequate trials of antidepressants based on the results of two large clinical trials.[6–8] Despite this, in 2006 the Centers for Medicare and Medicaid Services (CMS) made a noncoverage determination for VNS for MDD. This determination was based on a technology assessment that concluded that the VNS for MDD remained unproven/experimental because the large, randomized trial failed to meet its primary outcome measure of statistically significant antidepressant improvement 12 weeks after implantation. This effect of this decision was that Medicare, Medicaid, and most private insurers have not reimbursed for VNS for this indication. Ongoing efforts, specifically a 5-year, 800-patient naturalistic study comparing VNS with treatment as usual (TAU),[9] may lead to a re-evaluation of this policy, potentially increasing the availability of VNS for those with the most severe forms of TRD.

This article reviews the clinical development of VNS starting with the first recognition of its potential for treating depression, parses the results several large clinical trials, and suggests a future path for optimal clinical development and use.

EARLY DEVELOPMENT OF VAGUS NERVE STIMULATION

VNS was first developed and FDA-approved in 1997 for use in treatment-refractory epilepsy. Anecdotal reports of mood improvement seen in VNS-implanted epilepsy patients led to two open-label pilot studies tracking changes in mood. The first compared outcomes in 20 VNS-implanted epilepsy patients and 20 epilepsy patients who were not implanted with VNS but received stable anticonvulsant medication.[10] This study showed a significant reduction in depression scores within the VNS-implanted subjects ($P = .017$) but not a between-groups difference. Two potential significant limitations for this study were that on average, the two groups were not depressed; and the VNS group had significantly more baseline seizures per month compared with the control group. The second study reported on 11 patients implanted with VNS for medication-refractory partial complex seizures, who had at least a mild depression. These patients were then randomized to low- or high-dose stimulation.[11] Depression rating scores were done at baseline, 3 months, and 6 months. This group found statistically significant differences in several depression scores at both postimplant time points; however, only a trend toward significance between high- and low-dose stimulation ($P = .1$). Both studies also demonstrated that the decrease in depression scores was independent of the VNS antiseizure benefit.

THE VAGUS NERVE STIMULATION DEVICE

The primary VNS device used in the US and European clinical trials described next is the Neurocybernetic Prosthesis system now marketed by LivaNova (Houston, TX) (**Fig. 1**). The stimulus generator consists of a titanium-encased lithium battery that is