Vagus Nerve Stimulation: Back to the Future

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In this issue, Aaronson and colleagues (1) present compelling data from a 5-year observational study from the Treatment-Resistant Depression Registry, comparing two cohorts of patients with treatment-resistant depression, one that received implanted vagus nerve stimulation (VNS) therapy and another that either declined or could not afford VNS therapy and received treatment as usual only. The main findings from this study are important not only because the authors found that nearly 68% the VNS group met response criteria on the Montgomery-Åsberg Depression Rating Scale and over 43% met remission criteria, but also because almost 41% of the treatment-as-usual group met response criteria, and a quarter of these patients met remission criteria at some point over the 5-year study period. And so although there is a clear benefit for VNS both in terms of response and remission as well as a suggestion of benefit in terms of the maintenance of antidepressant effect, the outcomes from the treatment-as-usual group remind us that commonly employed pharmacotherapies and psychotherapies can be effective for some patients with treatment-resistant depression, sometimes after multiple failed attempts. It is therefore important for both clinicians and our patients to remain optimistic about the longer-term prognosis of patients with treatment-resistant depression.

There are important lessons to be learned from this study as well as the rest of the Cyberonics-funded VNS experience (1–5). The studies clearly remind us that the biological and psychological effects of treatment interventions in severely and chronically depressed patients may require many months of treatment to meet response and remission criteria that were initially operationalized in non–treatment-resistant patient populations. They also demonstrate that "one size—even a relatively profound intervention such as continuous stimulation of an afferent limb of the vagus nerve—will not fit (or cure) all" patients. There are other pragmatic lessons to be learned from the Cyberonics experience with VNS: First, many patients and their families did not embrace surgical implantation of a stimulator for depression as an acceptable treatment option, and second, the Centers for Medicare and Medicaid Services and many insurance companies had significant reservations about the cost and the benefit of VNS for depression. Even after receiving insurance approval for an implanted device, some patients and practitioners faced significant documentation hurdles that were required to justify the cost of ongoing monitoring and care. Fortunately, advances in technology and neurocircuitry may allow the field to use the Aaronson et al. study as a bridge between trials employing surgically implanted devices and studies of newer, noninvasive devices to stimulate the vagus nerve.

In spite of the limitations noted above, the development of implantable VNS devices has made important contributions to depression research and treatment. Although initially the use of vagus nerve stimulation was a serendipitous discovery, there has been increasing appreciation of the importance of the vagus nerve in health and disease (6–8). The vagus nerve has afferents to the brain through the nucleus tractus solitarius, which further connects to the amygdala, the frontal cortex, and other brain areas that play an important role in emotion regulation and have been implicated in depression (8). The vagus nerve also has afferents to the periphery, where it regulates a variety of processes, including inflammatory responses and sympathetic–parasympathetic tone (8). Thus, the vagus nerve has the ability to affect both brain processes and peripheral physiological functions that have been associated with depression as well as disorders associated with depression, such as cardiovascular disease. Intervention at this level holds promise for treating not only depression but also associated comorbid medical conditions.

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The development of a new generation of VNS devices has great promise for psychiatry. The new generation includes portable handheld devices that can deliver stimulation to the vagus nerve through the neck or the through the ear, via the auricular branch of the vagus nerve. Physiological studies have verified that these devices, with costs in the hundreds of dollars as opposed to thousands, reliably stimulate the vagus nerve in a way that affects central brain function (9). Noninvasive stimulation affects the A fibers of the vagus, which only go to the brain, not the C fibers, which project to the heart and other organs in the body. Nevertheless, pathways through the brain that have the potential to be beneficial in the treatment of depression also likely have projections to the periphery, with similar effects. Given the cost, risks, and inconvenience of surgical procedures, noninvasive VNS holds promise as a more widely applicable modality in psychiatry, and it should bring VNS into the realm

of alternatives to conventional forms of treatment like psychotherapy and pharmacotherapy, rather than being seen as a treatment of last resort. VNS also has other promising implications, like the ability to enhance learning and memory if applied at the time of new learning (10). Additionally, VNS results in a pattern of diminution of anxiety- and fear-related processes in the brain, with reduction of peripheral inflammatory and sympathetic activation processes in the periphery and the cardiovascular system, which suggests potential utility for a broad range of conditions that could be linked to stress and/or dysregulation of stress and inflammatory systems, such as irritable bowel syndrome, rheumatoid arthritis, and fibromyalgia, in addition to depression and other stress-related conditions like posttraumatic stress disorder. Therefore we may be on the verge of a new era in psychiatry, where electrical stimulation therapies take a seat at the table with other available therapeutic tools (9, 10).

In summary, this registry study provides important guidance about the longer-term impact of VNS in patients with treatment-resistant depression. The findings suggest that VNS may have a significant positive impact on illness course and prognosis for an as-yet not well characterized subset of patients with treatment-resistant depression. The data also demonstrate that implanted VNS has a reassuring safety profile and is well tolerated by a majority of patients. Thus, the report by Aaronson and colleagues is both a capstone for studies of implantable VNS devices and a harbinger of an exciting new opportunity for noninvasive VNS therapy for psychiatric disorders.

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