The Future Is Noninvasive: A Brief Review of the Evolution and Clinical Utility of Vagus Nerve Stimulation

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Vagus nerve stimulation (VNS) is a form of neuromodulation that stimulates the vagus nerve. VNS had been suggested as an intervention in the late 1800s and was rediscovered in the late 1980s as a promising treatment for refractory epilepsy. Since then, VNS has been approved by the U.S. Food and Drug Administration (FDA) for treatment of epilepsy, morbid obesity, and treatment-resistant depression. Unfortunately, VNS is underutilized, as it is costly to implant and often only suggested when all other treatment options have been exhausted. Discovery of a noninvasive method of VNS known as transcutaneous auricular VNS (taVNS), which activates the vagus through stimulation of the auricular branch of the vagus nerve, has reignited excitement around VNS. taVNS has immense potential as a safe, at-home, wearable treatment for various neuropsychiatric disorders. Major strides are being made in both invasive and noninvasive VNS that aim to make this technology more accessible to patients who would find benefit, including the ongoing RECOVER trial, a randomized controlled trial in up to 1,000 individuals to further evaluate the efficacy of VNS for treatment-resistant depression. In this brief review, we first discuss the early history of VNS; then its clinical utility in FDA-approved indications; and, finally, noninvasive VNS.

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DISCOVERY AND HISTORY OF VAGUS NERVE STIMULATION (VNS)

VNS is most commonly applied as an implantable form of brain stimulation that utilizes electrode cuffs that are wrapped directly around the left bundle of the vagus nerve and are connected to an implanted pulse generator in the chest (1). In its basic essence, VNS is simply electricity delivered to the vagus nerve, and it has been described in the literature for 125 years. The evolution of VNS began in a noninvasive format, transitioned to an invasive and implantable intervention, and only recently has reemerged in a noninvasive format. This review begins at the first reported use of electrical current administered to the vagus nerve.

In the late nineteenth century, Dr. James Corning, a neurologist in New York who was primarily researching cerebral blood flow and its involvement in epilepsy, created a carotid "electrocompressor" (2, 3), which was a fork-like instrument described in the archives of the National Library of Medicine. Corning believed that dysregulated cerebral blood flow caused seizures, and his device was intended to both compress and electrically stimulate the carotid sheath bilaterally. This is the first report of electrical stimulation of the vagus nerve for any intended medical purpose—more specifically, epilepsy. The device had early success both as an abortive measure to treat acute seizures and as a prophylactic in patients with epilepsy; however, these early studies were difficult to interpret, and this technique fell out of favor soon after Corning's death in 1923.

Although Corning's antiseizure device demonstrated promising behavioral effects, it remained unclear whether stimulation of the vagus nerve directly affected brain function by means of afferent projections. This question was addressed in 1938 by Bailey and Bremer (4), who investigated the cortical activation profile of VNS in a feline model using electrograms. They demonstrated that VNS activated orbitofrontal regions of the brain and, thus, likely has direct afferent projections to the brain that can be modulated with electricity. Zanchetti and colleagues (5) used a similar isolated encephalon feline model in 1952 to demonstrate that VNS reduces epileptic waveforms induced experimentally using strychnine. This was the first early finding to suggest that VNS may eliminate or temporarily suspend cortical hyperexcitability. Last, a research group administered VNS—again, in a feline model—and their findings suggested that VNS induced cortical synchronization and desynchronization (6), thus reconfirming VNS as a potential antiepileptic intervention.

Seminal work in VNS was conducted in the 1980s by Professor Jacob Zabara, who is credited with the invention of modern VNS. Zabara's group created implantable VNS systems, which they initially called the "neurocybernetic prosthesis device," and implanted these systems in canines with chemically induced seizures. As the seizure began, the device was turned on and seizure was terminated (7). This work was the impetus for modern VNS for epilepsy and, along with a more detailed follow-up replication study, demonstrated that the VNS antiepileptic effects were independent of stimulation laterality (8) and reconfirmed the antiepileptic utility of VNS.

These early VNS trials led to the first implantation of a human with a VNS device in 1988 by Penry and Dean who demonstrated reduction in seizure frequencies in three of four patients first implanted with VNS systems (9). Approval from the U.S. Food and Drug Administration (FDA) was granted for the marketing of VNS for epilepsy in 1997, after the pivotal trial in 310 patients demonstrated a 23% reduction in seizures after 3 months of VNS treatment (10, 11). FDA approval was subsequently granted to market the VNS device for depression in 2005 and for morbid obesity in 2015 (not discussed in this review). Clinical utility of VNS for epilepsy and depression are described in the following section.

CLINICAL UTILITY OF IMPLANTED VNS

The VNS implantation is a straightforward surgical procedure conducted in an ambulatory setting (1). After implantation, a trained physician programs the implanted device remotely and sets the stimulation intensity on the basis of comfort and tolerability, as well as titration to guideline effective parameters (current intensity, 0.25–3 mA; pulse width, 300–500 μs; frequency, 20–50 Hz; on time, 30–90 s; off time, 5–10 min). Once stimulation is turned on, it is tonically on until the battery is depleted (5 years) or the device is explanted. The patient also has a magnet that they can swipe over their chest to stop stimulation if they experience discomfort. There are limited side effects related to VNS, with the most reported side effect being hoarseness of voice or pain in the neck, both occurring during stimulation periods. These side effects can be managed by reducing VNS stimulation intensity.

Epilepsy

VNS was approved by the FDA in 1997 for treatment in adults with medically refractory epilepsy. Vagus nerve stimulators were implanted in patients with refractory partial seizures randomized to either a high-intensity or a low-intensity VNS therapy for 14 weeks (11). The primary objective was to show clinical utility and demonstrate that higher VNS stimulation intensities were more effective than lower intensities in reducing partial seizure frequency. Higher stimulation intensities reduced seizure frequency by 30.9%, whereas lower intensities only reduced mean seizure frequency by 11.3% (11). Furthering this work, DeGeorgio and colleagues (10, 12) demonstrated that patients with epilepsy who had been implanted with a VNS system had a median seizure reduction of 34% 3 months postimplantation, which increased to 45% at 1 year. Thirty-four percent of patients had a seizure reduction of more than 50%, whereas 20% of patients had a reduction of more than 75%. This study confirmed the effectiveness of VNS as treatment for patients with epilepsy.

Depression

VNS was approved by the FDA in 2005 for treatment in adults with severe recurrent depression. The discovery of the mood effects of VNS occurred as a result of anecdotal reports from patients implanted with a VNS system for epilepsy treatment (13). This led to the first prospective pilot study for mood—investigated in patients who had been implanted for epilepsy treatment—which took place shortly after data emerged, suggesting that patients with epilepsy who received VNS were seeing improvements in quality of life (14–16). The findings of the study revealed mild to moderate improvements in overall well-being and quality of life, including improvements in emotional adjustment and in cognitive and social functioning. Another study of the same generation found significant mood improvements of mild depressive mood disorders and negative symptoms in patients with epilepsy at the 3-month mark (16). Mood improvements were sustained at the 6-month follow-up and were independent of seizure control that was due to VNS (Montgomery-Asberg Depression Rating Scale [MADRS] score reduction of 3.8 points at 6 months).

The first prospective, randomized controlled trial (RCT) investigating the efficacy of acute VNS treatments was published in 2005 (17), in which 235 patients with nonpsychotic major depressive disorder or nonpsychotic, depression-phase, bipolar disorder received either active or sham VNS with treatment as usual. VNS was shown to be safe and well tolerated, and there was a response measured by the Hamilton Rating Scale for Depression (HRSD) in 15.2% of participants receiving active VNS treatment and in 10% receiving sham VNS. The study suggested that longer VNS treatment (more than 3 months) may be needed to measure an antidepressant response. In a naturalistic follow-up, a pattern of increasing antidepressant response and remission rates occurs as a function of overall duration of treatment (18).

The availability of VNS for treatment-resistant depression remains limited; however, there is a major ongoing research effort being conducted in conjunction with Medicare to ascertain the cost effectiveness and clinical utility of VNS for treatment-resistant depression in up to 1,000 patients. This trial, known as the RECOVER trial (ClinicalTrials.gov identifier: NCT03887715), is the largest prospective trial investigating the effectiveness of VNS for the treatment of depression. Findings from this clinical trial may make VNS

a more appealing line of therapy for patients with depression who have not seen improvement with conventional first-line interventions.

EMERGENCE OF NONINVASIVE VNS

On entering the 21st century, nearly 125 years after the first described VNS intervention, two of the biggest barriers to VNS are still its relatively high cost and invasiveness (19). These factors formed a challenge that kept researchers from conducting prospective follow-up trials in the clinical population as well as translating promising VNS findings from animals to humans. The need for an inexpensive, noninvasive way to stimulate the vagus nerve gave birth to a noninvasive form of VNS called transcutaneous auricular VNS (taVNS), which stimulates the auricular branches of the vagus nerve that innervate the human ears (20, 21).

Development of taVNS

taVNS was perhaps first suggested as a treatment for seizures in the literature by Ventureyra in 2000 (22) and is a fairly simple and inexpensive intervention (23). Unlike implanted VNS, all the components are external. Electrodes are affixed to the ear at surface landmarks predetermined to target the underlying auricular branch of the vagus nerve. An external pulse generator delivers electrical stimulation to the adhesive or clipped ear electrodes, which can be portable, self-administered, and delivered at home (23).

After solving the human ergonomics problem of creating these new systems that allow for fitting electrodes in and around the ear, along with advancements in electrode manufacturing, researchers began to address the fundamental question of whether taVNS was feasible and safe. taVNS safely uses low levels of electrical current to activate the central and peripheral nervous systems (24–26). Because of cardiac projections of the vagus nerve, however, several researchers addressed the concern of potential induction of bradycardia during taVNS sessions. Like cervical VNS, it is exceedingly rare that bradycardia events occur during taVNS (27, 28), and the only side effects seen are related to the administration of transcutaneous electrical current, which causes redness and skin irritation in some individuals at the site of stimulation (28).

In the development of new neuromodulatory interventions, it is important to determine optimal parameters for stimulation (29). A recent review of over 130 VNS and taVNS trials demonstrated the wide range of electrical wave form settings that can be used to treat neuropsychiatric disorders (30). The three critical parameter settings are pulse width, frequency, and intensity. There is a broad range of taVNS parameters (current intensity, 0.13–50 mA; pulse width, 20–500 μs; frequency, 1–30 Hz; on time, 0.5–1,800 s; off time, 30–270 s); often, these parameters are higher than the implanted VNS parameters. High parameter settings in implanted VNS not only risk increased discomfort to the patient but also risk damaging the nerve. Skin serves as an insulator for taVNS, which utilizes a wider range of investigated parameters, all of which seem to have similar safety profiles. In back-to-back studies, Badran and colleagues (31) investigated whether varying the frequency and pulse width would change the biological activity of taVNS in healthy individuals. Using heart rate as a biomarker, the authors demonstrated that higher pulse widths (250 μs and 500 μs), along with higher frequencies (10 Hz and 25 Hz), have larger effects on activating the vagus nerve and transiently reducing heart rate. This activation of the parasympathetic response is a key biomarker of determining vagal engagement and, thus, is a convenient marker of short-term response. Implanted VNS shares a similar biomarker (32), causing transient reductions in heart rate at higher parameter settings in the operating room; however, the patients do not receive therapy at those levels and, therefore, do not report reductions in heart rate during treatment.

Aside from parameter optimization and physiology investigations, groups attempted to determine whether the brain activation profile of taVNS mimicked that of implanted VNS. Several groups utilized functional magnetic resonance imaging (fMRI) to image the brain during implanted VNS (33, 34). These studies demonstrated that higher pulse widths and frequencies increased the brain response to VNS without changing the regional specificities. The commonly activated areas in response to implanted VNS were revealed as the prefrontal cortex, insula, caudate, putamen, hippocampus, cerebellum, and cingulate. Several groups followed these seminal VNS and fMRI findings in a similar fashion, but replaced implanted VNS with noninvasive VNS (35–38). These studies all reliably demonstrate that taVNS produces significant increased activation in the brain stem, hippocampus, amygdala, prefrontal cortex, thalamus, cerebellum, and cingulate. Although the afferent pathway of the auricular branch of the vagus nerve (ABVN) is still poorly understood, there is generally a consensus hypothesis that stimulation of the ABVN activates the main vagal afferent pathway (through the brainstem to upstream cortical projections).

Treatment of Epilepsy and Depression With taVNS

The clinical utility of taVNS is still in its infancy. The earliest clinical application of taVNS was suggested as a treatment for epilepsy, which is a logical extension of the early implanted VNS literature described earlier in this article. A randomized, double-blind, sham-controlled trial was conducted to determine these effects in what was known as the cMPsE02 trial by Bauer and colleagues (39). In 2016, they published their findings, which unfortunately were negative, having been unable to determine superiority of active taVNS versus sham control in 76 patients. Although disappointing, the use of a 1 Hz sham stimulation setting may have contributed to the large effect size of the sham-control group.

There have been several small depression trials using taVNS. Initially, in the 2013 study by Hein et al. (40),

patients were stimulated daily for two weeks, and taVNS was shown to reduce Beck Depression Inventory scores significantly in the active treatment group, compared with those in the sham-control group, but no effect on HRSD scores was found. Following this trial, Fang and colleagues (41) began to explore at-home taVNS for depression. Individuals self-administered either active taVNS or sham taVNS for 30 days at home, and this study revealed that HRSD scores were reduced significantly in the active taVNS group, compared with those in the sham-control group. fMRI conducted on these patients suggested that if significant brain activation is measured during imaging, it was associated with significant clinical improvement (HRSD scores) at the end of treatment (42). In a nonrandomized controlled study of taVNS in patients with mild or moderate depression, these findings were replicated, which demonstrated significant reductions in HRSD scores after 12 weeks of daily taVNS (43).

Because of its low cost and noninvasive nature, there is an expanding research field of taVNS that is exploring its use in several promising applications. These applications, although not covered in this review, include gastrointestinal conditions (44, 45), motor rehabilitation (46, 47), addictions (48), and psychiatric conditions (49, 50). There are also emerging closed-loop applications that pair taVNS with movement (51) and physiology (52).

CONCLUSIONS

At this time, VNS is undergoing a renaissance. Currently, the largest clinical trial in the world is underway, testing the utility of VNS for severe depression in up to 1,000 patients at 72 clinical sites in what is known as the RECOVER trial. Furthermore, noninvasive VNS is receiving increased coverage in the literature, with dozens of new applications and a simple and cost-effective means of translating the promising findings demonstrated in animal models of VNS. VNS was initially proposed as a noninvasive electrical stimulation intervention; 125 years later, it is, again, a noninvasive and exciting area of exploration. As VNS has broad applications in psychiatry, it is important to stay up to date on advancements in VNS research and to consider utilizing VNS as a treatment intervention if future trials demonstrate clinical utility.

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