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A Comprehensive Review of Vagus Nerve Stimulation for Depression

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Abstract

Objectives: Vagus nerve stimulation (VNS) is reemerging as an exciting form of brain stimulation, due in part to the development of its noninvasive counterpart transcutaneous auricular VNS. As the field grows, it is important to understand where VNS emerged from, including its history and the studies that were conducted over the past four decades. Here, we offer a comprehensive review of the history of VNS in the treatment of major depression.

Materials and Methods: Using PubMed, we reviewed the history of VNS and aggregated the literature into a narrative review of four key VNS epochs: 1) early invention and development of VNS, 2) path to Food and Drug Administration (FDA) approval for depression, 3) refinement of VNS treatment parameters, and 4) neuroimaging of VNS.

Results: VNS was described in the literature in the early 1900s; however, gained traction in the 1980s as Zabara and colleagues developed an implantable neurocybernetic prosthesis to treat epilepsy. As epilepsy trials proceed in the 1990s, promising mood effects emerged and were studied, ultimately leading to the approval of VNS for depression in 2005. Since then, there have been advances in understanding the mechanism of action. Imaging techniques like functional magnetic resonance imaging and positron emission tomography further aid in understanding direct brain effects of VNS.

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Authorship Statements

All listed authors contributed to the concept, design, writing, and revision of this manuscript. All authors approved the final manuscript.

Conflict of Interest: Dr. Bashar W. Badran and Dr. Baron Short own stock in Bodhi NeuroTech, Inc. Dr. Bashar W. Badran is a named inventor on brain stimulation patents assigned to the Medical University of South Carolina and serves as a consultant to companies that commercialize brain stimulation technology. All other authors have no conflict.

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Conclusions: The mood effects of VNS were discovered from clinical trials investigating the use of VNS for reducing seizures in epileptic patients. Since then, VNS has gone on to be FDA approved for depression. The field of VNS is growing, and as noninvasive VNS quickly advances, it is important to consider a historical perspective to develop future brain stimulation therapies.

Keywords

Depression; major depressive disorder; tVNS; taVNS; vagus nerve stimulation

INTRODUCTION

Vagus nerve stimulation (VNS) is an implantable form of neuromodulation that utilizes an implantable pulse generator within the chest of a patient and runs lead wires up to an electrode cuff wrapped around the cervical bundle of the left vagus nerve (1). This invasive neuromodulatory technique has been US Food and Drug Administration (FDA) approved for epilepsy, depression, and obesity. In the world of psychiatric neuromodulation, VNS is uncommon due to its cost, invasiveness, and lack of availability. VNS was FDA approved for treatment-resistant depression in 2005, but a noncoverage determination in 2007 from the Centers for Medicare and Medicaid Services has since significantly limited its availability as a treatment option (2). At the same time, transcranial magnetic stimulation (TMS) was being investigated to treat depression (3) and ultimately succeeded in becoming the primary brain stimulation intervention for depression.

Over the past decade, however, VNS has experienced a scientific renaissance. With the promising effects of noninvasive, transcutaneous auricular vagus nerve stimulation (taVNS) (4,5), researchers and companies are quickly trying to translate the prior success of implantable VNS into the taVNS space. With this rush to advance the next generation of noninvasive neurostimulation technology, it is critical to have a historical perspective to build upon. In this review, we provide a comprehensive historical prospective of implantable VNS in the context of its antidepressant effects and its development as a tool to treat depression. We address the history of VNS beginning with its origins and discovery as a potential instrument in the field of neuromodulation, as well as the science and data behind its proposed antidepressant mechanisms. In addition, we outline the history of trials leading up to FDA approval to treat major depressive disorder (MDD) and include a close examination on the optimization and mechanistic underpinnings of VNS.

EARLY HISTORY AND DEVELOPMENT OF VNS

The Invention of VNS

The origins of VNS date back to the late 19th century to the studies of New York neurologist James Leonard Corning (6). Based on the contemporary 19th century belief that seizures were due to abnormal cerebral blood flow (and treated by carotid compression), Corning developed a device that served two purposes. Later known as the Corning Fork, the fork-like device applied bilateral carotid compression and was used as an abortive measure to treat acute seizures in patients with epilepsy. In its second use, a procedure similar to current VNS, the (modified) fork was used to apply direct electric stimulation to the carotid sheath

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and was used as a prophylactic therapy for epilepsy. Indeed, the results of Coming's studies were difficult to interpret, but this did not disparage the scientific community, which would continue experiments with electrical stimulation of the vagus nerve into the next century.

An interest in electrical stimulation of the vagus nerve was revived in the first half of the 20th century. Based on previous studies investigating the cortical effects and localization of peripheral stimulation, a pair of scientists in Brussels (7) investigated the cortical localization of peripheral VNS in felines. VNS induced an acute increase in orbitofrontal activity with a delayed cortical depression response, thus demonstrating the afferent functions of the vagus nerve. A bradycardic and hypotensive corporeal response to stimulation confirmed the nerve's efferent functions. Findings from this study led to the electroencephalographical investigation of the vagus nerve and its projections conducted by Zanchetti and colleagues (8). While it was difficult to delineate localized effects of VNS in the feline cortex, the findings suggested that repetitive VNS was able to eliminate or reduce appreciably chemically induced cortical hyperexcitability. Seminal data like this most certainly paved the way for future studies exploring the antiepileptic effects of VNS.

Building upon existing anatomic and physiologic understanding of the vagus, a group in the 1960s more precisely explored the afferent projections of the vagus nerve. The group induced cortical synchronization and desynchronization by afferent cervical vagal stimulation in cats (9), thus confirming the potential of VNS as a future tool of neuromodulation. Only a year later, the same group continued to build from the conclusion that the afferent fiber groups of the vagus are structurally and functionally discrete. In a paradigm using abdominal VNS, the group discovered separate afferent systems that activated the cortex and were distinguished by conduction velocity (10). While this did confirm that afferent VNS does modify the cortical and subcortical electroencephalogram, researchers were still far from an answer explaining the precise functions of the different bundles within the nerve itself.

Modern VNS for Epilepsy

The 1980s marked a huge step forward in the history of VNS and its path toward therapeutic indications. In a seminal study conducted by Prof. Jacob Zabara, seizures were chemically induced in canines and were therapeutically terminated using a neurocybernetic spectral discrimination device that selectively activated neurons inhibitory to hypersynchronous discharge (11). In short, chemically induced seizures were terminated within seconds via VNS. The first of its kind, this study laid the basis for further development of an antiepileptic device targeting the vagus nerve.

In a more detailed follow-up, Zabara (12) explained a mechanism of direct repetitive electrical stimulation of the vagus nerve to terminate strychnine-induced seizures and PTZ-induced tremors in dogs. The findings, which were not dependent on laterality of stimulation (bilateral vs. unilateral and left vs. right), laid the groundwork for future human studies by confirming the antiepileptic potential of VNS. This study was built on the cumulation of all the studies previously discussed and the idea that the vagus nerve consists of more afferent fibers than efferent. At the same time, early clinical VNS studies were underway, attempting to translate this novel antiepileptic paradigm to human subjects.

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VNS was approved by the FDA in 1997 to treat adults with medically refractory epilepsy. From the research conducted prior to its approval as well as the data produced upon its establishment as a therapy for epilepsy, clinicians and researchers started to notice incidental findings in the patients they were treating for refractory epilepsy. While future studies continued to confirm the safety and efficacy of VNS in its treatment of epilepsy, beneficial side effects were noted in some patients leading to further investigation of the vagus nerve's ability to modify quality of life and mood. The first studies to look at these incidental results are described below.

Discovery of the Mood Effects of VNS

An early example of these incidental yet beneficial side effects were noted by one team's attempt to treat epileptic encephalopathies using vagal nerve stimulation in a pediatric population (13). The team monitored patients for two years following implantation of the VNS device. While VNS did not offer any benefit to patients in terms of seizure duration or frequency, it did offer an indirect benefit in several areas. Unrelated to seizure control, VNS was associated with an improvement in perceived side effects and general behavior for the whole group. This was thought to be due to a direct action of VNS on behavior, concentration, and affect.

Ben-Menachem and colleagues (14) studied the levels of amino acids and other metabolites in the cerebrospinal fluid of patients with partial seizures who were receiving VNS, comparing levels before and after three months of stimulation. The study's finding that total and free levels of inhibitor gamma-aminobutyric acid were increased while excitatory glutamate levels were diminished could be an interesting discussion in a review geared toward epilepsy; however, 5-hydroxyindoleacetic acid levels were also increased after three months of vagal nerve stimulation. The findings suggest that there is a serotonergic modulation with VNS and it may play a role in the antidepressant effects of VNS.

The first prospective pilot study for mood in epilepsy patients took place shortly after data emerged suggesting that epilepsy patients receiving VNS were seeing improvements in quality of life (15-17). Morris and colleagues conducted a double blind study assessing cognition and quality of life changes in epilepsy patients receiving VNS at standard clinical doses for seizures (15). While the group did not find any changes in cognition, the findings of the study suggested mild improvements in quality of life and sense of well-being on several different measures (QOLIE-31, SF-36, WPSI), with the most significant improvements seen in areas like concentration, emotional adjustment, and cognitive/social functioning. Studies such as this one led to further investigations of the effect VNS has on mood, emotions, and well-being.

The first prospective trial comparing the mood effects of antiepileptic drugs (AEDs), with and without VNS, found that the population receiving VNS had significantly improved mood scores compared to those receiving AEDs alone (16). These findings confirmed the frequently seen clinical anecdotes of an association between VNS and mood improvement in epilepsy patients. Another study of the same generation found significant mood improvements of mild depressive mood disorders and negative symptoms in epilepsy patients at the three month mark (17). Mood improvements were sustained at six-month

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follow-up and seemed to be independent of seizure control due to VNS (Montgomery-Asberg Depression Rating Scale [MADRS] scores of 10.8 ± 5.0, 7.8 ± 3.8, and 7.0 ± 3.6 at baseline, three months, and six months, respectively, $p < 0.05$). Dosing remained an unanswered question at that time. The culmination of VNS research led to clinical trials to further quantify antidepressant effects with VNS. In the forthcoming sections, we take a closer look at the path of VNS to FDA approval for treatment-refractory depression.

THE PATH TO FDA APPROVAL FOR DEPRESSION

Early Prospective VNS Trials for Depression

In the 2000s, a wave of research was published showing positive results and revealing a tremendous potential for VNS and the treatment of depression. In a study that was the first of its kind, VNS was investigated as a therapeutic modality to treat major depressive episodes, episodes that were specifically treatment refractory and had failed multiple medication trials (18). In a four-site prospective trial, the potential antidepressant effects of VNS were assessed by delivering stimulation to severely depressed and nonpsychotic individuals ($N = 30$), either in a major depressive episode or individuals with bipolar disorder who were currently in a depressive episode, via an implantable NeuroCybernetic Prosthesis System. Following implantation, a two-week single-blind recovery period (no stimulation during this time) was followed by ten weeks of VNS. Participants were allowed to take standard of care medications as long as the medication and dose remained consistent at baseline and at the end of the 12-week trial period. The study also included long-term follow-up at 9 and 12 months. Findings showed reductions in depression scores, suggesting that VNS had antidepressant effects. They found a 40% response rate, using a 50% reduction in the baseline Hamilton Depression Rating Scale (HDRS) total score to define response (HDRS of 38.0 ± 5.5 at baseline and 23.0 ± 10.8 at the end of the acute phase). In the responders, these effects were sustained following the acute phase. However, there were no significant correlates of VNS response found and the study was limited by small sample size and the absence of a control group. Interestingly, the study suggested that the failure of response to prior electroconvulsive therapy (ECT) may be a possible predictor of failure of responding to VNS.

In an extension of the study described above, 30 additional patients with treatment-resistant depressive episodes were included in an open pilot study to analyze efficacy, side effects, and clinical predictors associated with response to VNS in treatment-refractory depression (19). The study found a 30.5% response rate, with response defined as a greater than 50% reduction in HDRS scores. In addition, the number of failed antidepressant treatment trials had a strong association with a positive VNS outcome (improvement in mood). Findings suggested that VNS was suitable for those with mild–moderate treatment-resistant depression (TRD), not severe cases. As an extension of this open pilot, the same 30 patients (19) received an additional nine months of VNS treatment following completion of the three months acute study (20). The participants were followed at three, six, and nine months after the three-month acute study. This extension study found that symptomatic improvements were sustained (40%–46% of the original participants remained responders) over nine additional months of longer-term VNS treatment (91% of responders at three-month acute

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study end remained responders at 12 months) and that remission rates significantly increased (three nonresponders at three months acute study exit became responders at 12 months—17%–29%; $p = 0.045$). The rationale for a randomized controlled trial was building, and the path to FDA approval was starting to unfold.

In a two years naturalistic follow-up from the aforementioned studies, it was found that most of the response to VNS (based on Hamilton Depression Scores) occurred within the acute phase (first three months after initiating treatment), with some additional improvement at the 12 month mark (21). However, within the group that responded acutely, improvements in depressive symptoms were sustained through 24 months. Response rates were sustained more than the two-year period and were not significantly different at 12 and 24 months. The study was limited by a naturalistic follow-up design, small sample size, and absence of a control group. By this time, the VNS world was ready for a randomized and controlled trial.

Randomized Controlled Trials for Depression

As the results of the open trial described above became available, the gears behind a randomized and controlled trial were already moving. The first randomized and controlled trial investigating the efficacy of acute VNS treatments was published in 2005 (22). A total of 235 patients with nonpsychotic major depressive disorder or nonpsychotic, depressed phase, bipolar disorder were enrolled in this trial comparing ten weeks of masked adjunctive VNS to sham treatment. The other major requirement to be enrolled was to have failed a minimum of two, up to six, medications prior to enrollment (treatment-resistant depression). VNS was shown to be safe and well tolerated but did not demonstrate evidence of short-term efficacy for adjunctive VNS in treatment-resistant depression, likely due in part to the study being underdosed. It is important to note that dosing in this trial was limited to 1 mA, while doses of up to 3 mA are used in epilepsy patients. There was a marked response in the Hamilton Depression Rating Score in both active VNS (15.2% reduction) and sham VNS (10% reduction). The study suggested that longer VNS treatment (greater than three months) may be needed to measure an antidepressant response.

An answer to the largest question lingering after the first randomized controlled trial appeared later that year in a naturalistic follow-up of the study discussed previously (23). In this follow-up study, the same treatment-resistant depression patients were analyzed over the year following the acute phase of treatment. The study showed a pattern of growing response and remission rates at 3, 6, 9, and 12 months following initiation of VNS treatment (HDRS mean of 28.0 ± 5.7 at baseline, 19.6 ± 9.7 at 12 months, $p < 0.001$). VNS was well tolerated and a new theme in VNS for depression was emerging—there could be a long-term cumulative benefit of using VNS to treat treatment-resistant depression that may not be noticed with only acute VNS.

A European open label study found similar accumulated antidepressant effects as the ones produced with VNS in the randomized controlled trial above (24). Researchers analyzed response and remission rates in 74 treatment-resistant depression patients more than a 12-month period using Hamilton Depression scores. Response rates increased from 37% at 3 months to 53% at 12 months and remission rates increased from 17% at 3 months to 33%

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at 12 months. The time course of VNS and its mood improving effects were becoming more evident and the results were reproducible.

In 2005, VNS was FDA approved for the treatment of major depressive disorder. Less than 200 years after Coming's fork stimulated the carotid sheath, a similar device had been created and developed as treatment for two debilitating disorders, epilepsy and major depression. The early part of the 21st century saw the fruition of years of labor-intensive science and research. The fields of psychiatry and neurology were becoming more intertwined with the approval of two neuromodulation tools for the treatment of depression (TMS and VNS) and the future was promising for researchers continuing to study and develop these tools.

A seminal study in the history of VNS was published by Aaronson and colleagues in 2017 (25). This five-year study was a prospective, open-label, nonrandomized, observational trial that included 795 patients who were experiencing a major depressive episode (unipolar or bipolar depression) of at least two years' duration or had three or more depressive episodes (including the current episode), and who had failed four or more depression treatments (including electroconvulsive therapy). The VNS group in this study had better clinical outcomes than the treatment as usual group, as evidenced by a significantly higher five-year cumulative response rate (67.6% compared with 40.9%) and a significantly higher remission rate (cumulative first-time remitters, 43.3% compared with 25.7%). The impact from studies such as this one certainly contributed to the future of VNS and laid the groundwork for future trials like A Prospective, Multi-Center, Randomized Controlled Blinded Trial Demonstrating the Safety and Effectiveness of VNS Therapy® System as Adjunctive Therapy Versus a No Stimulation Control in Subjects With Treatment-Resistant Depression (RECOVER) trial described below.

As we write this manuscript, there is ongoing major research effort using VNS to treat depression with a planned enrollment goal of 6800 patients (ClinicalTrials.gov Identifier NCT03887715). This study, conducted in conjunction with Medicare, hopes to determine efficacy and cost effectiveness of VNS for TRD. LivaNova received US Centers of Medicare & Medicaid Services approval to start the RECOVER clinical trial in 2019 and patients are being randomized to sham VNS or real VNS in the blinded portion of the study, subsequently participants will receive real VNS in an open-label longitudinal arm. However, there will be several differences in this trial compared to the initial 2005 trial for FDA approval. The blinded portion of the study will be 52 weeks (compared to 10 weeks for the FDA approval trial) and doses up to 3 mA will be allowed (compared to 1 mA in the FDA approval trial). This study, if positive, would likely provide the evidence needed for Centers for Medicare and Medicaid Services coverage for VNS in TRD.

FURTHER DEVELOPMENT AND REFINEMENT OF VNS FOR DEPRESSION

Recent Developments

Between 2005 and 2017, more than 3000 papers were published concerning predinical and clinical VNS and the treatment of epilepsy or depression (26). Issues regarding dosing and parameters were more understood (parameters discussed in a different review) and the

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chemical and neurological mechanisms of VNS were being proposed and confirmed by the plethora of research being published (mechanisms discussed in the next section of this review). Despite the great leaps of progress being made, some were still cautious to promote VNS as an efficacious therapy in the treatment of depressive disorders. And despite the substantial evidence regarding VNS and its efficacy in treatment-resistant depression, critics remained hesitant.

There has only been one prospective RCT to compare VNS treatment to placebo or sham treatment conducted by Rush and colleagues in 2005 (22). Since then, the only other prospective, randomized, controlled trial was a dose finding study published in 2013 (27). In this study, all of the 331 participants had failed at least four antidepressant medication trials, while 97% of participants had failed at least six antidepressant medications. The participants were split into three groups: low, medium, and high dose. Frequency and duty cycle were kept the same between all three groups. A pulse width of 250 μsec was used in the medium and high-dose groups while a pulse width of 125 μsec was used in the low-dose group. The output current varied between all groups: 0.25 mA for low, 1.0 mA for medium, and 1.5 mA for high. The study took place over a course of 50 weeks, with an acute phase that lasted 22 weeks, after which they could increase output current. The study found all three groups to have significant improvement in depressive symptoms at the end of the acute phase. The improvements were better sustained by the medium and high-dose groups at the end of the longer-term phase (50 weeks). The study's findings made an interesting point—even the low-dose group had significant antidepressant effects. Using low-dose VNS as a sham treatment may be an issue, as even low-dose VNS provides a substantial antidepressant effect disqualifying it as a controlled sham for study.

A 2013 meta-analysis of the modern VNS clinical trials compared active VNS paired with treatment as usual (TAU) to TAU alone (28). The measures used in these newer trials were the Montgomery-Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression-Improvement (CGI-I) scale. The meta-analysis found a consistent superiority of VNS and TAU together over TAU alone. A more recent systematic review and meta-analysis showed that the antidepressant effects of VNS improved to 24 months and safety issues were minimal (29).

Another important study by Conway and colleagues (30) in 2018 explored the effects of VNS on quality-of-life measures in patients receiving chronic VNS for depression. This multicenter, longitudinal study found significantly improved quality of life (as measured by the Q-LES-Q-SF) along with a reduction in depressive symptoms (as measured by the MADRS) in chronic VNS patients compared to treatment as usual. In fact, this study highlighted the association between VNS and quality of life, even when reductions in depressive symptoms were less than the 50% normally used to describe a "response."

Noninvasive VNS

Historically, one of the biggest barriers to VNS, both from a research and clinical perspective, was its high cost and invasiveness (31). Although we do not cover noninvasive VNS in this manuscript, it is important to consider the recent development of taVNS (32,33). This new, noninvasive form of VNS stimulates the auricular branch of the vagus

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nerve, a distal offshoot of the main bundle of the vagus nerve that innervates the human ears (34,35). taVNS has been demonstrated to mimic the neurophysiological effects of implanted VNS (36-38) and has made the translation of the promising effects of VNS possible.

taVNS is appealing as it is noninvasive, portable, and can be self-administered in the home. For those reasons, there are early studies exploring the effects of taVNS on depression (31,39,40), with modest effect sizes reported. The taVNS field is still in its infancy, with a lack of consensus or understanding of the optimal parameter and dosing recommendations that may provide optimal behavioral outcomes. With that caveat, it may still be early for prospective RCTs using taVNS for depression; however, this may be a promising treatment option within the next decade.

UNDERSTANDING THE MECHANISM OF VNS

Early studies of VNS suggest that norepinephrine plays a critical role in VNS effects. Norepinephrine and the locus coeruleus are well documented and helped guide research attempting to understand the mechanism and physiology of VNS (41). Looking back to our understanding of the vagus nerve and the fact that 80% of its fibers are afferent (projecting inward), we remember that the vagus nerve projects to the solitary nucleus of the medulla, and then projects to the median dorsal raphe nucleus and the locus coeruleus, key areas of serotonergic and noradrenergic innervation (42). Both of these areas (and both serotonin and noradrenaline) are thought to play major roles in the pathophysiology of depression. As stated previously, early studies found increased levels of 5-hydroxyindoleacetic acid, a major serotonin metabolite, in the cerebrospinal fluid following VNS (14). Later studies also found increases in serotonin and noradrenaline following long-term VNS (43). With a basic understanding of vagal anatomy and its afferent projection, we enter the age of neuroimaging and all of its potential.

Concurrent VNS/fMRI

Functional neuroimaging emerged as a promising way to measure the direct brain effects of VNS. In 2001, Bohning and colleagues were the first to overcome the technological challenge of simultaneously delivering VNS while acquiring functional neuroimaging. Bohning's synchronized VNS-functional magnetic resonance imaging (fMRI) study investigated neurophysiologic effects and responses of VNS in nine patients who had previously been implanted with neurocybernetic prosthesis (NCP) devices for treatment-resistant depression (44). The study found a way to monitor the signal from the implanted NCP system with an external computer to determine the exact timing of the VNS cycle and was able to capture and synchronize a reference stimulus from the device and the corresponding blood oxygenation level-dependent fMRI (BOLD-fMRI) images in synchrony with it. The NCP system was programmed to 7 sec on and 108 se off. An internal reference, a control auditory signal (440 Hz tone) was also added to control for somatosensory confounds. VNS-induced activity was found in the orbitofrontal and parieto-occipital cortexes bilaterally, the left temporal cortex, the hypothalamus, and the left amygdala.

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A next step in understanding the brain's response to VNS was to assess whether there was any dose dependency in a similar study using an interleaved VNS and BOLD-fMRI paradigm to assess regional cerebral blood flow resulting from application of 7 sec of either 20 Hz or 5 Hz vagal nerve stimulation (45). VNS frequency and dosing effects on spatial brain activation patterns were analyzed. There were three preliminary findings. First of all, the study confirmed previous VNS/fMRI findings of neuroanatomy effects on the hypothalamus and orbitofrontal cortex (both involved in mood disorders) found by Bohning (44); 20 Hz VNS increased BOLD fMRI response in those regions. The study is also consistent with VNS frequency and dose effects on bilateral regions of the brain—high frequency 20 Hz and higher stimuli. VNS increased BOLD fMRI response and at the same level of statistical significance, there was no brain activation at 5 Hz—so differences in VNS could be due to frequency or total stimuli or both. Lastly, VNS potentially has a dose-dependent modulating effect on brain activity.

Similar to the study above where the frequency of the VNS dose was varied between subject groups, (46) Mu et al. conducted a BOLD-fMRI trial investigating the effects of manipulating pulse width on the neurophysiological response. Three different pulse widths were used in 12 adults with major depression. Three fMRI/VNS scans were performed, each scan randomly assigned one of the three pulse width designations. Importantly, this study assessed acute VNS stimulation response in subjects exposed to prolonged VNS. Varying the stimulus pulse width (130, 250, or 500 μsec) demonstrated an increased BOLD signal in the left lateral orbital cortex at all three pulse widths. Global activations for pulse widths of 250 μsec and 500 μsec were both significantly greater than that induced by a pulse width of 130 μsec but not significantly different from each other. For global deactivation, pulse widths of 130 μsec and 250 μsec were both significantly greater than pulse width 500 μsec but not significantly different from each other. Data confirm that VNS at 130 μsec produces significantly less activation when compared to 250 and 500 μsec. Data also support that a pulse width of 500 μsec globally produces no more activation compared to 250 μsec.

Concurrent VNS/PET

The first study published looking at regional cerebral blood flow (rCBF) changes associated with four weeks of VNS treatment came shortly after the initial fMRI studies (47). They measured rCBF twice by single photon emission-computed tomography (SPECT) 99mTc-hexamethyl-propylene amine oxime: once during the baseline period before implantation and then again after four weeks of VNS treatment. Decreases in rCBF were found in several brain regions including the amygdala and the left hippocampus. An increase in rCBF was found in the left prefrontal cortex. These patterns of rCBF alterations share features with rCBF findings in patients who were administered Selective Serotonin Reuptake Inhibitors (SSRIs). When compared with antidepressant treatment, VNS decreased rCBF in the right thalamus, while antidepressant treatment was found to be associated with either decreased rCBF in the left thalamus or increased rCBF in the thalamus bilaterally. The rCBF changes in response to VNS therapy were different from rCBF findings in response to ECT, meaning VNS may have its own specific antidepressant mechanism.

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As we increased our understanding of the mechanism of VNS, we found that it correlated with our understanding of the pathophysiology of mood disorders. The same areas that were responding to the antidepressant effects of VNS treatment were the same areas described to be abnormally functioning in mood disorders. A study that continued to build on its predecessors used positron emission tomography (PET) to analyze rCBF changes during cVNS in four female patients with medically refractory depressive disorders (48) which demonstrated that VNS induced increases in rCBF in the prefrontal and frontal regions and decreases in rCBF in limbic regions.

Neuroplasticity

Monoamines and neurotrophic factors may play a key role in the development and treatment of depressive mood disorders. In rat studies, it had already been found that acute VNS was associated with global upregulation of neurotransmitters (like norepinephrine) and increased gene expression of neurotrophic factors like brain-derived neurotrophic factor (BDNF) and fibroblast growth factor (bFGF) (49). Neurotrophic factors may mediate the antidepressant response, as well as mediating neurogenesis in key areas involved in mood disorders like the hippocampus (50).

This evidence was given further support by a study investigating the effects of VNS on hippocampal volumes in treatment-resistant depression patients (50). In responders to pharmacological and nonpharmacological (i.e., ECT) antidepressants, an increase in hippocampal plasticity had already been reported. In this study, an increase of left and right hippocampal volumes was found, which paralleled the clinical response. These findings indicate a fundamental role of hippocampal volumes as a marker of response to VNS in TRD and further support the proposed mechanisms of VNS and other antidepressant therapies.

While the theory of VNS and its mechanism undergoes further development, other forms of neuromodulation may offer clues to the mechanism of this tool’s antidepressant effects (51).Treatments like transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) point to the role of the brains’ dopaminergic system and its role in their ability to treat depression. Further exploration of this area will likely yield more clues in the search for answers regarding the mechanism of VNS.

CONCLUSIONS

In order to develop future therapies, it is always important to consider the context provided by the past. As described, VNS has a long and winding history, with VNS research having been conducted for over a century. Surprisingly, there is still a lack of consensus on optimal stimulation parameters, dosing considerations, and mechanism. VNS has slowly evolved over time and as we enter an era of noninvasive alternatives, we must use this history to build upon the knowledge and understanding of implantable VNS to create new interventions for depression and other neuropsychiatric disorders.

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