Personalized Medicine in Psychiatry 17–18 (2019) 32–36

Contents lists available at ScienceDirect

Personalized Medicine in Psychiatry

journal homepage: www.elsevier.com/locate/pmip

Predictors of response for vagus nerve stimulation in treatment-resistant depression☆

V.C. de Leon[a], A.T. Drysdale[a], C.R. Conway[a], S.T. Aaronson[b,*]

[a] Washington University School of Medicine, 660 S. Euclid Ave, Campus Box 8134, St. Louis, MO 63110, United States
[b] Sheppard Pratt Health System, 6501 N. Charles Street, Towson, MD 21204, United States

ARTICLE INFO

Keywords:
Treatment-resistant depression
Vagus nerve stimulation
Antidepressant response predictors
Bipolar depression

ABSTRACT

The past 20 years have witnessed the emergence of several new and effective neurostimulation treatments for depression. Stimulation of the left cervical vagus, or Vagus Nerve Stimulation (VNS), originally employed in treatment refractory seizure disorders, is emerging as a hopeful option to treat patients with highly treatment-resistant depression (TRD). Several clinical trials have demonstrated that a significant subset of highly refractory TRD patients experience an antidepressant response to VNS; one that is typically sustained. Although VNS in TRD is relatively new, existing studies support that certain TRD patient characteristics, as well as treatment delivery, can influence the likelihood of an antidepressant outcome. Existing data supports that VNS is effective: equally for bipolar versus unipolar TRD, in highly resistant patients (studies suggest antidepressant efficacy even in patients who have failed as many as 8 or more medications), as well as for patients suffering from prolonged depression. Failure to respond to electroconvulsive therapy (ECT) likely decreases the likelihood of response to VNS; however, many patients failing ECT do still respond. Clinical trial data to date also support that higher electrical current/charge delivered over time likely contributes to sustained antidepressant response. Brain imaging studies support that overactive insular cortical activity, as well as hypoactive orbitofrontal cortical activity, decreases likelihood of response. Finally, although concomitant personality disorder has not been studied in VNS antidepressant effectiveness trials, existing consensus indicates that severe concomitant personality disorder likely diminishes response. Additional studies need to be done to assess predictors of response of VNS in TRD.

1. Introduction

Intermittent electrical stimulation of the left cervical vagus nerve (termed "vagus nerve stimulation" [VNS]) was first studied in treatment refractory epilepsy (TRE) [1]. During early studies of VNS in TRE, researchers noted that epilepsy patients with concomitant major depressive disorder (MDD) experienced improvements in depressive symptoms. Subsequent studies in TRE assessed these improvements and found that reductions in mean depressive scores were independent of anti-seizure benefit [2,3]. This led to open label studies to investigate whether VNS would be effective in treatment-resistant depression (TRD). These early unblinded TRD studies demonstrated that a subset of VNS patients experienced a sustained antidepressant response to VNS [4–6]. This was followed by a randomized controlled trial of 235 patients who had failed 2 to 6 adequate trials of antidepressant treatment in which all subjects were implanted with a VNS device but only half were turned on in the first twelve weeks [7]. While not meeting its primary outcome measure of a significant separation in Hamilton Depression Rating Scale (24 item) between active and sham treatment following 8 weeks of optimized stimulation ($p = 0.251$), a secondary outcome measure, the 30 item Inventory of Depressive Symptoms Self Report (IDS-SR30) did demonstrate a significant difference ($p = 0.032$). In retrospect, the most critical problem with the study design of this trial was the timing of the primary outcome measure being only twelve weeks after VNS implantation. Further, four of those twelve weeks were at suboptimal dosing: two weeks of surgical recovery (no stimulation), and two weeks of stimulus titration (ramping up the electrical current). Hence, TRD patients in this study only received 8 weeks of "optimal" stimulation. Subsequent open label follow-up data from this study, as well as from an open-label European study, demonstrated that longer,

☆ This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
* Corresponding author.
E-mail addresses: deleonv@wustl.edu (V.C. de Leon), adrysdale@wustl.edu (A.T. Drysdale), conwaycr@wustl.edu (C.R. Conway), saaronson@sheppardpratt.org (S.T. Aaronson).

https://doi.org/10.1016/j.pmip.2019.05.001

Available online 30 May 2019

sustained stimulation was required to maximize antidepressant response: a gradually increasing response rate was observed over depression evaluations at 3 months, 6 months, 9 months and 12 months [8,9]. The current thinking is that most TRD patients require between 6 and 12 months stimulation to demonstrate an antidepressant response.

On the basis of this randomized controlled trial, in 2005, the United States Food and Drug Administration (FDA) approved VNS for the treatment of patients with TRD who had failed 4 adequate dose-duration oral antidepressant trials. Nonetheless, using the failure to separate on the primary outcome measure in the randomized controlled trial, in 2007, the United States Center for Medicare and Medicaid Services (CMS) issued a noncoverage decision, which led to most private medical insurance companies also deciding not to reimburse for the VNS device and surgical implantation for TRD. Hence, from 2007 to the present, many TRD patients wanting a trial of VNS were not able to afford this treatment. Additionally, VNS for TRD has been approved by many healthcare regulatory agencies throughout the world, including the European Union, Australia, Canada, and several nations throughout Central and South America.

However, as part of the FDA approval, the manufacturer of the VNS device, LivaNova (then called Cyberonics) agreed to create a TRD Registry that would collect open label data on 800 patients followed over five years, 500 of whom had the device implanted compared to 300 getting treatment as usual (TAU) without VNS. This registry, first reported on in 2017, provides the largest and longest longitudinal dataset collected on TRD [10]. The positive outcomes for VNS in severely treatment resistant patients (all TRD patients were required to have 4 documented adequate dose-duration failed antidepressant trials; mean ~ 8) led to CMS re-opening its non-coverage decision in 2018 and proposing “coverage with evidence development” (CED) in the form of a new randomized controlled trial that CMS will in part support.

With the reemergence of this novel treatment for TRD, many clinicians, having little/no experience with VNS in TRD, do not know what makes a TRD patient a “good candidate” for VNS. Existing data, especially through the large registry studies, provides some insight into the factors that may contribute to the likelihood of response to VNS. This paper highlights the existing knowledge of some of the known predictors of VNS response. These are summarized in Table 1.

2. The vagus nerve stimulation device

While there is active research into external methods of VNS stimulation [11] the best evidence base for TRD is stimulation with an implantable device. The primary VNS device is the Neurocybernetic Prosthesis® system now marketed by LivaNova. The stimulus generator consists of a titanium encased, lithium battery-powered stimulator that is implanted under the skin in the upper chest wall. Pig-tailed electrodes emerge from the device, are tunneled under the skin, and are then wrapped around the left cervical vagus nerve. The device is implanted under general or local anesthesia typically in 1–2 h. Two weeks following the surgery the device is activated and set by a wand, held over the skin covering the device (much like programming a cardiac pacemaker); this wand is connected to a handheld programming device. The telemetric programming wand sets the four stimulation parameters for the device: current (from 0.25 to 3.0 mA), stimulation frequency (from 20 to 50 Hz), pulse width (from 130 to 500 ms) and duty cycle (adjustable from the usual settings of 30 sec. on and 5 min. off). The initial settings are gradually titrated up, usually over the first two weeks of treatment as tolerated by the patient. While the mechanism of action of VNS in TRD is not fully established, several animal studies and human neuroimaging studies demonstrate significant changes in regions known to be associated with depression (prefrontal and cingulate cortex, as well as brainstem) following chronic treatment [12]. Clinical and neuroimaging studies support that the effects of VNS in TRD occur gradually [8,13]: significant improvements in mood may take as long as six months to develop and continue to improve beyond that time up to about 2 years [6].

3. Target VNS population

The recent TRD Registry included only patients who had failed at least 4 antidepressants over the course of their illness [10]. This is a level of treatment resistance beyond the scope of most existing clinical trials. Additionally, TRD patients with bipolar depression, who had failed ECT in the current episode, had been depressed for greater than three years, or suffered from co-morbid anxiety were included (all standard exclusion criteria most other clinical trials with the exception of deep brain stimulations trials [14]). While some conflicts persist about the definition of TRD, it is also clear that TRD represents a continuum of severity of illness, [15] and that greater efforts must be made to find pathways to improve the lives of patients [16] especially those with no evidence-based alternatives. Regardless of these conflicts, there is little question that existing VNS for TRD studies have enrolled the “sickest of the sick”.

To date, only some 5000 VNS devices have been implanted for patients with depression. Hence, it is hard to offer many clear recommendations with this limited experience base. The overall good news is that several factors contributing to treatment resistance have a limited effect on treatment outcomes as will be explored below. In addition, given that the length of time it takes for VNS to affect a response, this treatment clearly is not the treatment of choice for acute management of severe depressive illness (i.e., acute suicidality).

4. Severity and chronicity of illness

Several factors go into assessing the severity and chronicity of depression—how many years someone has been ill, how long the current episode has lasted, how high the depression rating scale score is at baseline and how many treatment interventions the patient has had an inadequate/failed response to (both in the current episode and over the entire course of their illness). All of these variables were collected in the aforementioned VNS Registry study as well as most other VNS studies. It is safe to assume that higher levels of treatment resistance, severity, and chronicity will make response and remission more elusive, but the

Table 1
Factors for candidacy for VNS for TRD.

Factors that favor potential good candidacy for VNS	Factors that suggest against candidacy for VNS
Proper Indication Diagnosis: Treatment resistant unipolar or bipolar depression	Need for acute management or rapid response for depressive illness (e.g., acute suicidality)
History of verified antidepressant treatment resistance (FDA indication = 4 antidepressant treatment failures) [10]	Presence of severe comorbid personality disorder
Maximal tolerated electrical current (associated with greater likelihood of sustained antidepressant benefit) [17]	Severe self-harm and/or repeated suicidal attempts
Absence of severe comorbid personality disorder	Unrealistic expectations
Willingness to have implanted device and ability to undergo implantation surgery	
Prior Response to ECT [10]	

illness burden for the VNS Registry patients was impressively high. There was no exclusion criterion for too many years depressed or too many failed treatments. For example, for the VNS registry the mean illness duration for implanted patients was about 20 years, 41% of the group had been depressed longer than 5 years (in the current episode), the mean number of verified treatment failures was 8.2, and the mean baseline Montgomery-Åsberg Depression Rating Scale score at baseline was 33.1, consistent with a marked to severe depression. Despite this severe illness burden, 67.8% of the VNS implanted patients met response criteria at some point during the five year follow-up (compared to 43% of the TAU group). This figure was only slightly less (61.7%) if the patient has been in the same depressive episode for over five years at baseline (compared to 39.1% of the TAU group). While a sub-analysis was not reported for the number of failed trials vs. response rate, one can assume that more failures would suggest a somewhat poorer outcome.

4.1. Unipolar versus bipolar depression

There is a paucity of FDA approved treatments for bipolar depression. Neurostimulation, including VNS, may provide unique support for this condition. Thus far, there have been no prospective, comparative trials of VNS efficacy in unipolar versus bipolar TRD. However, the studies of VNS to date support the conclusion that this treatment has similar antidepressant efficacy in unipolar and bipolar TRD. All existing large trials of VNS in TRD have included patients with both unipolar and bipolar depression (e.g. [4,7,8,10,17]. The initial study of VNS in TRD [4] included 9 bipolar I or II patients among the 30 participants. A logistic regression analysis of response predictors found no significant impact of unipolar versus bipolar diagnosis on treatment response. Similarly, subsequent larger studies, which also included unipolar and bipolar TRD patients, identified an equivalent response pattern. Rush et al., [7] studied 235 TRD patients, including 25 with bipolar disorder, for 10 weeks with VNS versus sham treatment and did not report any difference in response rate by diagnosis. The authors reported absolute response rates of 13.1% in unipolar depression and 8.7% in bipolar depression. Using the extension phase of the Rush et al. [8] study population, Nierenberg and colleagues [18] performed a 12-week sham-controlled VNS trial prior to open-label treatment and found no difference in treatment response between unipolar and bipolar TRD patients after 2 years of treatment. In the TRD registry described above, Aaronson and colleagues [10] followed TRD patients receiving VNS for five years of open-label observation. In their cohort, 134 of 494 patients were diagnosed with bipolar TRD. As with unipolar depression, they found significant depressive symptom improvement in patients with bipolar TRD at all intervals from 12-month through 60-month follow-up [10]. VNS represents a potentially efficacious option for both unipolar and bipolar TRD.

As with any depression treatment, it is reasonable to monitor for the emergence of manic symptoms during VNS. A recent case report details two patients previously diagnosed with unipolar depression who developed manic symptoms at 8 and 9 months after initial stimulator placement [19]. In larger clinical trials to date, there is a small but nonzero reported rate of mania emergence during VNS treatment. Rush and colleagues [8] tracked VNS patients naturalistically with open-label treatment over one year. During this period, three patients experienced manic symptoms during VNS treatment. One of these patients had a prior diagnosis of bipolar disorder, one had a prior history of treatment-induced mania, and a third was previously diagnosed with unipolar depression. All three episodes resolved during the study's observation period, though the latter required hospitalization and pausing stimulation until the episode ended [8]. Therefore, VNS for TRD shows a low but nonzero risk of mania emergence. As with administration of any novel antidepressant treatment, clinicians should routinely monitor VNS patients for manic symptoms.

5. Concomitant personality disorders

Chronic depression is frequently associated with personality disorders. One of the greatest challenges faced in neurostimulation treatments for psychiatric illness is determining the degree to which comorbid personality disorders influence psychiatric illness, and when to utilize neurostimulation treatments when concomitant personality traits/disorders are influencing the individual's response/lack of response to antidepressant treatment. This is particularly true when the treatment is more invasive, as is the case with VNS, and involves the permanent placement of a stimulation device. Though patients can have the devices subsequently explanted if they do not respond to treatment, this could be particularly traumatic in patients who have less established coping mechanisms. Hence, our experience has suggested that patients with *severe* personality disorder history should not be implanted with VNS devices. Because individuals with chronic depressive illnesses are often difficult to tease out from individuals with personality traits/disorders, this is admittedly a difficult decision. Among the criteria that argue *against* VNS device placement would be a history of chronic and severe self-mutilation, history or repeated suicide/parasuicidal attempts, unrealistic expectations, poor frustration tolerance (given the long timespan to see positive effect), and history of severely tumultuous interpersonal relationships. In the end, this is a clinical judgment call.

6. Past history of ECT

VNS is not the only neurostimulation therapy treatment option available to those with TRD. Electroconvulsive therapy (ECT), considered the "gold standard" of antidepressant treatments in TRD, is a common treatment modality that many patients try prior to advancing to other options. Existing studies support that response to ECT predicts response to VNS in TRD. In a prospective, open-label, five year observational study conducted by Aaronson [10], highly resistant TRD subjects from the TRD registry with a mean of 8.2 failed trials received either treatment as usual (TAU; any treatment available to treating psychiatrist) or TAU with adjunctive VNS. In a sub analysis of this study, the investigators compared antidepressant response rates in TRD patients who had previously responded to ECT and those TRD patients who had not. Of those who had previously responded to ECT (N = 290 VNS arm; N = 109 in TAU arm), the VNS group had a statistically significant greater cumulative response rate (71.3%) than those ECT-responders who received TAU (56.9%; $p = 0.006$). On the other hand, when analyzing subjects who had *not* responded to ECT, 59.6% in the adjunctive VNS arm had a response compared to 34.1% of the TAU arm ($p < 0.001$). Hence, response to ECT in the past appears to increase the likelihood of responding to VNS in the future; however, failure to respond to VNS does not preclude antidepressant response to VNS. In fact, the percentage of patients who had failed to previously respond to ECT but responded to adjunctive VNS (59.6%) was comparable to the percent of patients responding to TAU only who had previously *responded* to ECT. VNS remains a potential alterative to ECT responders and nonresponders, though previous response to ECT seems to favor response to VNS. ECT responders who require maintenance ECT may represent a special population who may get extraordinary benefit from a chronic neurostimulation paradigm like VNS.

7. Electrical parameters

Much like antidepressant pharmacotherapies, evidence supports that neurostimulation treatments have optimal electrical parameters [20,21]. Hence, studies have been done to assess if certain electrical parameters are predictive of better antidepressant outcomes in VNS. In VNS, there are several modifiable electrical parameters including: current (mA), frequency (Hz), pulse width (μs), and duty cycle (seconds device is on and minutes device is off). In earlier studies of VNS, the

parameters used were reflective of those used in VNS trials of TRE. For example, an early study of VNS in TRD by Rush et al. [8] used an initial current of 0.25 mA titrating up to an average current of 0.67 mA, a frequency of 50 Hz, a pulse width of 500 μs, and a duty cycle of 30 s on and 5 min off. This resulted in 48% of subjects receiving ≤ 0.50 mA and 52% received > 0.50 mA. Clinical experience and subsequent studies have suggested that higher current was desirable, and that higher frequency (greater than 20 Hz) and greater pulse width (greater than 250 μs) were associated with greater patient discomfort; hence, there has been a movement towards lowering these two parameters in TRD patients, which allows increases in current without discomfort. To assess which VNS electrical "dose" was optimal for antidepressant effects in TRD, a double blinded, randomized trial was conducted by Aaronson et al. [17] to analyze antidepressant response rate in low, medium and high current doses in a sample size of 331 TRD subjects with two phases. The initial phase included a blinded, initial 22 weeks in which TRD patients were randomly assigned to either "low", "medium", or "high" electrical parameters. In the remaining 25 weeks, patients were allowed to have their current doses increased. The target settings during the blinded phase (first 22 weeks) were: 1) "low dose"; output current 0.25 mA; pulse width 130 μs (n = 102); 2) "medium dose"; output current 0.5–1.0 mA; pulse width 250 μs (n = 101); and 3) "high dose"; output current of 1.25–1.5 mA; pulse width of 250 μs (n = 107). Of note, the titration phase for each dose consisted of 4–6 weeks (targeted 4 weeks, allowed up to 6 weeks). During the blinded initial phase, all three groups had significant mean drops in standardized depressive scores following the start of stimulation ($p = 0.0023$) and by week 22, 20% of all TRD patients had a 50% or greater drop in depression scores (classified as "treatment responders"). Surprisingly, there was no significant difference in antidepressant response rate between dose groups at the end of the 22 week blinded phase. However, by the end of the study (following week 50), there was evidence that assignment to either the high dose or medium dose group predicted sustained antidepressant response (less relapse) than assignment to the low dose group. This suggested that the greater the exposure to higher current was associated with overall lower depressive scores, which prompted a regression analysis comparing depression scores and charge delivered. This sub analysis demonstrated that increased current was associated with decreased depressive scores ($r = -0.21$, $p < 0.001$). As a result, the current thinking is that the goal should be to take the patient to the highest tolerable electrical current to maximize likelihood of antidepressant benefit and lower the risk of depression relapse.

8. Brain imaging

Though our understanding of how VNS brings about antidepressant effects in the brain remains limited, study of brain imaging may reveal some clue as to which patients may respond to VNS in TRD. Conway et al., [22] used fluorodeoxyglucose positron emission tomography (FDG-PET) to study if baseline (pretreatment) cerebral mean regional glucose uptake (CMRGlu) predicted antidepressant response at 12 months. Selecting four regions of interest known to be critical in depression: dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and anterior insular cortex (AIC), this group assessed the correlations between baseline CMRGlu in these regions and antidepressant change in 15 TRD patients receiving VNS for 12 months. This group determined that lower anterior insular cortex CMRGlu ($p = 0.004$) and higher orbitofrontal cortex CMRGlu ($p = 0.047$) together predicted HDRS change ($R^2 = 0.58, p = 0.005$). In a whole brain, voxel-wise analysis, baseline CMRGlu in the right anterior insular cortex correlated with change in depressive symptoms ($r = 0.78$, $p = 0.001$). These findings suggest that baseline anterior insular (low) and orbitofrontal cortex metabolic activity (high) may positively influence antidepressant outcomes at 12 months.

9. Conclusion

VNS represents a novel intervention for patients with severe TRD for whom there have been few alternatives to ECT. In choosing to use VNS, clinicians should be careful with patient selection. It takes months to see full benefit; hence, patients needing an acute intervention (e.g., acute suicidality) would not be considered likely VNS candidates. So as to set reasonable outcome expectations, patients should be well informed about the long duration it may take to see benefit. Clinical experience does support the notion that many chronically depressed patients see tremendous benefit from even sub-response level improvement in a depression rating scale, a notion clarified by Conway et al. 2018 [23], which found clinically meaningful quality of life improvements starting at a 34% drop in a MADRS score. Patients requiring maintenance ECT may represent a unique group who require maintenance neurostimulation, which can be achieved from an implanted device. Most optimistically, studies support that VNS has demonstrated efficacy in the most severely treatment refractory depressed patients, even patients who have failed ECT, multiple medications trials, and have been depressed for many years.

References

[1] Salinsky MC, Uthman BM, Ristanovic RK, Wernicke JF, Tarver WB. Vagus nerve stimulation for the treatment of medically intractable seizures. Results of a 1-year open-extension trial. Vagus Nerve Stimulation Study Group. Arch Neurol 1996;53:1176–80.

[2] Harden CL, Pulver MC, Ravdin LD, Nikolov B, Halper JP, Labar DR. A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. Epilepsy Behav 2000;1:93–9.

[3] Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res 2000;42:203–10.

[4] Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. Biol Psychiatry 2000;47:276–86.

[5] Marangell LB, Rush AJ, George MS, Sackeim HA, Johnson CR, Husain MM, et al. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. Biol Psychiatry 2002;51:280–7.

[6] Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby SH, et al. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. J Clin Psychiatry 2005;66:1097–104.

[7] Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry 2005;58:347–54.

[8] Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. Biol Psychiatry 2005;58:355–63.

[9] Schlaepfer TE, Frick C, Zobel A, Maier W, Heuser I, Bajbouj M, et al. Vagus nerve stimulation for depression: efficacy and safety in a European study. Psychol Med 2008;38:651–61.

[10] Aaronson ST, Sears P, Ruvuna F, Bunker M, Conway CR, Dougherty DD, et al. A 5-year observational study of patients with treatment-resistant depression treated with vagus nerve stimulation or treatment as usual: comparison of response, remission, and suicidality. Am J Psychiatry 2017;174:640–8.

[11] Mertens A, Raedt R, Gadeyne S, Carrette E, Boon P, Vonck K. Recent advances in devices for vagus nerve stimulation. Expert Rev Med Devices 2018;15:527–39.

[12] Carreno FR, Frazer A. Vagal nerve stimulation for treatment-resistant depression. Neurotherapeutics 2017;14:716–27.

[13] Conway CR, Chibnall JT, Gebara MA, Price JL, Snyder AZ, Mintun MA, et al. Association of cerebral metabolic activity changes with vagus nerve stimulation antidepressant response in treatment-resistant depression. Brain Stimul 2013;6:788–97.

[14] Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, et al. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. Biol Psychiatry 2015;78:240–8.

[15] Conway CR, George MS, Sackeim HA. Toward an evidence-based, operational definition of treatment-resistant depression: when enough is enough. JAMA Psychiatry 2017;74:9–10.

[16] Rush AJ, Aaronson ST, Demyttenaere K. Difficult-to-treat depression: a clinical and research roadmap for when remission is elusive. Aust N Z J Psychiatry 2018. 4867418808585.

[17] Aaronson ST, Carpenter LL, Conway CR, Reimherr FW, Lisanby SH, Schwartz TL, et al. Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: acute and chronic effects. Brain Stimul 2013;6:631–40.

[18] Nierenberg AA, Alpert JE, Gardner-Schuster EE, Seay S, Mischoulon D. Vagus nerve stimulation: 2-year outcomes for bipolar versus unipolar treatment-resistant depression. Biol Psychiatry 2008;64:455–60.

[19] Salloum NC, Gott BM, Conway CR. Sustained remission in patients with treatment-resistant depression receiving vagal nerve stimulation: a case series. Brain Stimul 2017;10:997–1000.
[20] Isenberg KE, Dinwiddie S, Heath AC, Osborne V, Tepper M, Jarvis M, et al. Effect of electrical parameters on ECT convulsive threshold and duration. Ann Clin Psychiatry 2016;28:105–16.
[21] Stern WM, Tormos JM, Press DZ, Pearlman C, Pascual-Leone A. Antidepressant effects of high and low frequency repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex: a double-blind, randomized, placebo-controlled trial. J Neuropsychiatry Clin Neurosci 2007;19:179–86.
[22] Conway CR, Chibnall JT, Gangwani S, Mintun MA, Price JL, Hershey T, et al. Pretreatment cerebral metabolic activity correlates with antidepressant efficacy of vagus nerve stimulation in treatment-resistant major depression: a potential marker for response? J Affect Disord 2012;139:283–90.
[23] Conway CR, Kumar A, Xiong W, Bunker M, Aaronson ST, Rush AJ. Chronic vagus nerve stimulation significantly improves quality of life in treatment-resistant major depression. J Clin Psychiatry 2018;79.