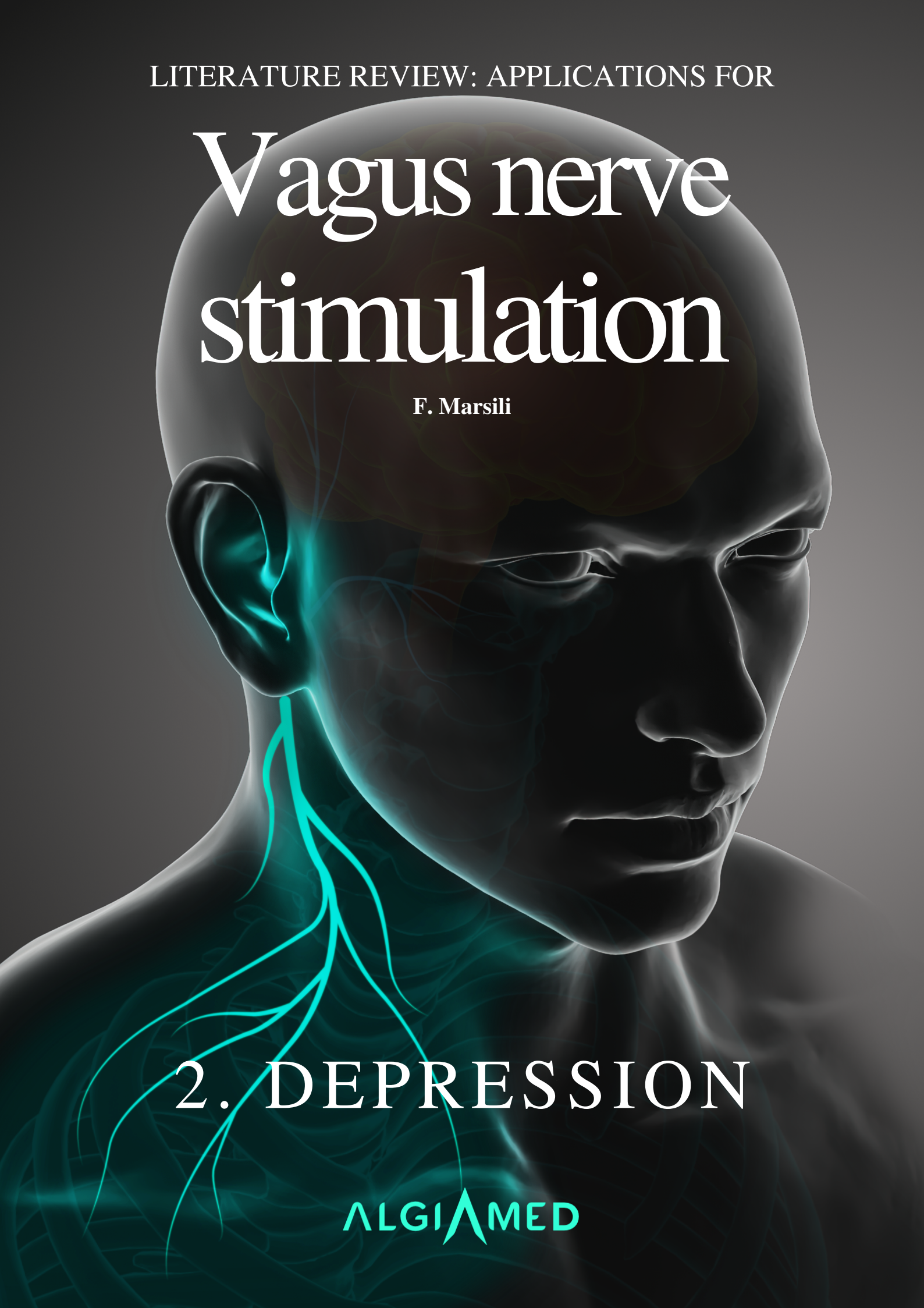
LITERATURE REVIEW: APPLICATIONS FOR

Vagus nerve stimulation

F. Marsili



2. DEPRESSION

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Author's choice

The papers in this collection focus on the application of Vagus Nerve Stimulation (VNS) as established therapeutic solution for difficult-to-treat conditions.

The vagus nerve is the longest cranial nerve and is widely distributed throughout the body, traversing the neck, thorax and abdomen. It is composed by motor fibres and sensory fibres from sympathetic and parasympathetic branches. [1], [2]. Afferent branches of the vagus nerve innervate brain behavioural areas involved in depressive states, and it desynchronises cortical activity with anti epileptic effects [3], [4]. Efferent branches of the vagus nerve regulate gastrointestinal secretory and motor function [5]. Recent advances in the field, have unraveled an anti-inflammatory role of the efferent vagus nerve via the Cholinergic Anti-inflammatory Pathway (CAP), a known mechanism for neural inhibition of inflammation linked to the activation of the autonomic nervous system (ANS) [6], [7].

Electrical stimulation of the VN modulates the nervous system at central, peripheral, and autonomic levels without the need for pharmacological interventions. For decades, invasive techniques of VNS have demonstrated their clinical efficacy in VN-related diseases and, to these days, efforts have been made to create a more safe, effective, and non-invasive solution to VNS.

The auricular branch is the only peripheral branch of the VN on the human body, it is part of the afferent portion of the VN that directly connects to the brainstem. Thus, auricular VN has become the most favourable access point for non-invasive VNS. Neuroimaging studies on animal models and humans have confirmed the modulatory efficacy of auricular VNS (aVNS). For examples, fMRI studies show identical activation patterns in the brain between invasive and aVNS, with significant inhibitory and anti-inflammatory effects. Due to the existence of different control systems, the anti-inflammatory effects of aVNS (i.e., release of norepinephrine and noradrenaline, and neurotrophic factors) seem to occur immediately after intervention, while neuroplastic changes only occur as a consequence of sustained regenerative efforts [7].

Colleciton 1 and collection 2 are the most extensive selections, since VNS has been standard-of-care for epilepsy and depression for decades. Collection 3 explores the possibility of using VNS for the treatment of posttraumatic stress disorders. Collection 4 focuses on fibromyalgia and collection 5 on multiple sclerosis. Collection 6 and 7 corroborates the hypothesis that VNS can be used to activate the cholinergic anti-inflammatory pathway to treat inflammatory diseases, such as inflammatory bowel disease or rheumatoid arthritis. Collection 8 and 9 focus on the use of VNS for ameliorating pain sensitivity in chronic pain conditions and for rehabilitating upper limb motor fibres after ischemic strokes, respectively. In conclusion, collection 10 opens up other possibilities for clinical applications of VNS, ranging from cardiovascular diseases, through ADHD disorders, to tinnitus.

To summarise, VNS is a novel technology and its non-invasive configuration is still under investigation. Further clinical examinations are mandatory in order to understand the underlying mechanism of VNS and to open the door to new possible therapeutic applications. However, being a non-invasive, safe, and efficient therapeutic solution, VNS is an attractive tool for further implementation and new creative clinical applications.

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2. VNS and depression

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REVIEW

Vagal Nerve Stimulation for Treatment-Resistant Depression

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Abstract Major depressive disorder (MDD) is prevalent. Although standards antidepressants are more effective than placebo, up to 35% of patients do not respond to 4 or more conventional treatments and are considered to have treatment-resistant depression (TRD). Considerable effort has been devoted to trying to find effective treatments for TRD. This review focuses on vagus nerve stimulation (VNS), approved for TRD in 2005 by the Food and Drugs Administration. Stimulation is carried by bipolar electrodes on the left cervical vagus nerve, which are attached to an implanted stimulator generator. The vagus bundle contains about 80% of afferent fibers terminating in the medulla, from which there are projections to many areas of brain, including the limbic forebrain. Various types of brain imaging studies reveal widespread functional effects in brain after either acute or chronic VNS. Although more randomized control trials of VNS need to be carried out before a definitive conclusion can be reached about its efficacy, the results of open studies, carried out over period of 1 to 2 years, show much more efficacy when compared with results from treatment as usual studies. There is an increase in clinical response to VNS between 3 and 12 months, which is quite different from that seen with standard antidepressant treatment of MDD. Preclinically, VNS affects many of the same brain areas, neurotransmitters (serotonin, norepinephrine) and signal transduction mechanisms (brain-derived neurotrophic factor–tropomyosin receptor kinase B) as those found with traditional antidepressants. Nevertheless, the mechanisms by which VNS benefits patients nonresponsive to conventional antidepressants is unclear, with further research needed to clarify this.

Keywords TRD · VNS · BDNF-TrkB · Monoamines

Both worldwide and in the USA, major depressive disorder (MDD) is quite prevalent. In the USA, the lifetime prevalence is about 30%, with the yearly prevalence being almost 9% [1]. Although antidepressant drugs are effective, their effect is mild to moderate, with selective serotonin reuptake inhibitors having effect sizes for acute response of 0.20 to 0.40; their ability to prevent relapses or recurrences is better, with effect sizes of 0.6 to 0.7 [2]. Another way to state this is that after 2 adequate trials with antidepressants, only about half the patients achieve remission, being defined as a ≥ 50% decrease in a severity rating scale score and a very low final score indicating minimal residual symptoms (see [3]). Remission is now viewed as the "gold standard" for treatment outcome as those with less residual symptoms after treatment for depression subsequently have less depressive symptoms, and better social functioning than those with more residual symptoms [4–6]. Just as importantly, up to 35% of patients with nonpsychotic MDD do not respond to 4 or more conventional treatments [7]. Such patients are considered to have treatment-resistant depression (TRD). Establishment of effective treatments for TRD would be very useful given the large number of patients who have it, their diminished quality of life and health [8, 9], the increased cost associated with it [9], and the overall chronic course of both MDD and TRD [10, 11].

In view of such facts, much attention has been focused on trying to establish treatments that would at least have a

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modicum of effectiveness in such nonresponsive patients, either as standalone or adjunctive treatment. This review covers one such treatment, vagus nerve stimulation (VNS). It begins with a review of the evidence for its effectiveness and concludes with a review of effects it produces on brain function. A variety of neuromodulation techniques in addition to VNS have been tried in TRD, for example deep brain stimulation and repetitive transcranial magnetic stimulation. There are varying levels of evidence for their acute and long-term efficacy, as well as their safety (see [12]). Nevertheless, the Food and Drugs Administration approved VNS for treatment of TRD in 2005 and repetitive transcranial magnetic stimulation in 2008. The Food and Drugs Administration approved VNS as an adjunctive long-term treatment of chronic recurrent depression in patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments. It is important to note that the approval is for long-term treatment as the data reviewed below show efficacy to improve over months and even years but to be more limited over the first several months.

Interest in this topic has generated a number of review articles mentioned later. Most of these focus on clinical efficacy. Those that reviewed efficacy as well as potential mechanisms of action were published over a decade ago. This review covers both topics. Furthermore, it takes the position as discussed later, that the efficacy of VNS has to be compared with the response over time of patients with TRD not receiving VNS.

The Vagus Nerve and VNS

There is both an anatomical and functional rationale for stimulating the cervical vagus nerve to treat diseases of the brain. Since 1937, the vagus has been known to be mixed nerve with about 80% of its fibers carrying sensory afferent information to the brain and having about 20% efferent motor fibers [13]. Early evidence for the functionality of its afferent projection was the observation that its stimulation caused electroencephalography changes [14]. Its name comes from the Latin word for "wandering" owing to its having such a course along the esophagus and arteries to innervate numerous peripheral organs and structures (see [15]). Its visceromotor efferent component originates in the dorsal motor nucleus of the medulla, whereas the initial termination point of its afferent fibers in brain is primarily the nucleus tractus solitarius (NTS), also in the medulla. Neurotransmitters used by vagal afferents include peptides such as substance P and calcitonin gene-related peptide and the excitatory amino acid transmitter L-glutamate.

The major outputs from the NTS can be characterized as 1) local projections to medullary motor nuclei; 2) projections to the midbrain including the locus coeruleus (LC), dorsal raphe nucleus (DRN) and other brainstem interneurons in the reticular formation and to the parabrachial nucleus (PBN); and 3) projections to forebrain sites such as the hypothalamus, amygdala, bed nucleus of the stria terminalis (BNST), and insular cortex (see [15–17]). And of course, there are projections from nuclei such as the LC and DRN to limbic forebrain areas. Thus, areas in brain long thought to be involved in behaviors relevant for depression are innervated, either directly or indirectly, from projections of afferent vagal fibers terminating in the NTS.

The VNS procedure involves implantation of a stimulation generator connected to bipolar electrodes that are placed around the left vagus nerve. The rationale for stimulating the left vagus nerve for TRD (or epilepsy) is that it innervates the AV node of the heart so as to have less of an effect on heart rate than the right vagus, which innervates the SA node. Stimulation of each vagus nerve produces effects on heart rate consistent with such innervation [18, 19]. Further, the bipolar stimulating electrode is configured with the cathode at the proximal lead and the anode at the distal lead so as to direct action potential propagation to the central nervous system by creating an anodal block at the distal lead. This procedure is carried out as day surgery with local or general anesthesia. In the USA, such surgery is usually done by a neurosurgeon. The stimulation device is activated telemetrically by a wand connected to a hand-held computer. Stimulation parameters used include current (mA), frequency (Hz), pulse width (μs), and duty cycle (the duration that stimulation is on or off). Such parameters reflect the "dose" of VNS. Stimulation is usually started with a low current, 0.25 to 0.75 mA, which can be increased gradually. Frequencies on the order of 20 to 30 Hz are used clinically as frequencies of 50 Hz or higher can damage the vagus [20]. A pulse width of 250 μs and a duty cycle of stimulation for 30 s on/300 s off is often used.

Clinical Studies

As reported in Penry and Dean [21], VNS was used originally from 1988 to 1989 for inpatients with treatment-resistant epilepsy. In 2000, Elger et al. [22] were the first to note improvement of mood in patients with epilepsy that was independent of their seizure attenuation. Since 2005, almost 3000 clinical and preclinical papers dealing with VNS have been published, with many concerning its use in epilepsy or depression.

Given the importance of "dose" in producing a beneficial therapeutic response, it is somewhat surprising that the only prospective study examining dose of VNS for therapeutic outcome in TRD occurred quite recently, in 2013. Aaronson et al. [23] compared the response of patients with TRD to adjunctive VNS over 22 or 50 weeks and used 3 different "doses". The frequency and duty cycle were the same across the 3

groups, whereas stimulation in the "low" group was 0.25 mA current with a 130 μs pulse width. For the "medium" group, the parameters were 0.5 to 1.0 mA and 250 μs, whereas it was 1.25 to 1.50 mA and 250 μs for the "high" group. This study was a double-blind, randomized comparison of the effect of the different doses of VNS, but there was no control group (sham stimulation). The high dose was associated with less tolerability although 70% to 75% of patients in the high group reached their assigned dose. Similar efficacy was found in the 3 dose groups, that is, differences in outcome measures were not statistically significant. However, after 22 weeks of treatment, 10% to 20% of patients in the low group responded (depending on the scale used for efficacy) whereas 19% to 31% of patients did so in the high group. Consistent with data described below, behavioral improvement continued over time in that 25% of the patients who had not responded at 22 weeks did so at 50 weeks. Importantly, response was sustained up to 50 weeks in those who responded at 22 weeks, especially those receiving medium or high doses. Muller et al. [24] carried out a retrospective analysis of the effectiveness of 2 different doses of VNS in 2 groups of patients: 1) a low-strength/high-frequency (≤1.5 mA, 20 Hz) group *versus* a high-strength/low-frequency (>1.5 mA, 15 Hz) group. Change in the Hamilton Rating Scale for Depression (HAMD) at 6-month intervals was the outcome measure. Better outcome was achieved with the low-strength/high-frequency group. Further prospective studies are clearly needed as there is evidence that VNS does have frequency-dependent effects in patients, as shown by results using functional magnetic resonance imaging (fMRI) [25].

In addition to original studies of the efficacy of VNS in TRD, there have been quite a few reviews of this topic [16, 26–34]. And, not surprisingly, the overall conclusion is that more research, particularly randomized control trials (RCTs), is needed before efficacy can be established conclusively. This is so, but our opinion is that the evidence for efficacy is quite substantial in that its effect has to be compared with the response over time of depressed patients resistant to treatment not receiving neurostimulation therapies such as VNS. And that response is quite modest. Dunner et al. [35] reported a prospective study of outcomes of 124 patients with TRD (15 of whom were bipolar) treated with standard care [i.e., treatment as usual (TAU)] over 2 years. After 12 months, the response rate was about 12% and it was 18.4% after 24 months. Remission rates were 3.6% and 7.8%, respectively. And neither response nor remission was well-maintained over time with TAU. The emphasis on RCTs with VNS is likely based, in part, on the high placebo response rates in clinical trials of antidepressants. In such short-term trials, placebo response rates of almost 40% are usual [36]. Although placebo responses may be maintained for 12 weeks after stopping the clinical trial [37], maintaining recurrent depressives on placebo over 6 to 12 months is much less effective than maintaining them on drug [38]. Further, the current poor response of patients with TRD to TAU is noteworthy in light of the increase in placebo response rates since the 1980s to 1990s in nontreatment-resistant patients [39]. Thus, even though there is clearly a need for more long-term RCTs with VNS, the data reviewed below on patients with TRD should be considered in this context.

Based on results of earlier open trials of the short-term (10 weeks) efficacy of VNS in patients with TRD that showed response rates of 30% to 40% [40, 41], an RCT of 10 weeks of treatment with VNS *versus* sham stimulation was carried out [42]. On the primary HAMD response measure, VNS produced a response rate of 15.2% *versus* 10.0% in the sham group—this was not a significant difference. However, differences in response rates with a secondary outcome measure were significant. To date, this is the only RCT to employ sham stimulation as a comparison to VNS. Attention has been focused appropriately on this negative result and the fact that there is considerable variability in effectiveness among the studies [30]. And longer-term studies (e.g., 2 years) with VNS (reviewed below) can be influenced by the natural course of MDD. For example, Nahas et al. [43] followed the 59 patients in the original open 10-week study of Sackeim et al. [41] for 2 years. Response rate increased over time from 31% at 3 months to 42% to 44% at 12 to 24 months. Remission rates were about 25% after 1 to 2 years. And for those that responded at 3 months, 50% to 75% remained well at 12 to 24 months. Subsequently, with a larger cohort of 205 patients, of those who responded to VNS at 3 months, 76.7% maintained response at 24 months and for those who did not respond until 12 months, 65% were still responders at 24 months [44]. For patients with TRD, these response and remission rates are considerably higher than those achieved over a similar time with TAU [35] such that the natural course of treatment-resistant patients is different from those receiving treatment who are not resistant, where recovery rates of 60% to 85% are seen over 2 years [45, 46].

George et al. [47] attempted to put such results from this open trial into perspective by analyzing data from those treated with VNS for 1 year in open studies with results from comparable patients receiving TAU as reported by Dunner et al. [35]. Although there was not *a priori* randomization, the patient characteristics seem comparable with similar inclusion and exclusion criteria and demographics, with the studies being carried out over a similar time period. Also, 12 of the 13 sites for the TAU study participated in the VNS + TAU study with 9 additional sites only participating in the VNS + TAU study. Irrespective of the method of data analysis, the addition of VNS to TAU produced a greater reduction of depressive symptoms with the effect of VNS becoming greater the longer the treatment. Importantly, the effect of VNS was sustainable in that about 55% of those who responded in the VNS group

were also responders at 12 months, whereas this percentage was only 11.5% in the TAU group.

Results similar to these from the USA were found in an open-label study enrolling patients with TRD from 6 European countries. Seventy patients were evaluated at 3 months with 60 at 12 months [48] and 49 at 24 months [49]. In the initial report [46], response rates of 37% and 53% were found after 3 and 12 months, respectively, whereas remission rates at these times were 13% and 33%, respectively. In the follow-up 2-year study [47], 53% fulfilled the response criterion and 39% did so for the remission criterion [49]. Furthermore, a reanalysis of this study was carried out by Christmas et al. [50] in which only patients who had failed 4 or more antidepressant trials were included. Here, a response rate of 35.7% was found after 12 months, somewhat lower than that found in the entire patient sample. Once again, initial response was reasonably well-maintained over time with almost 40% of those responding at 3 months still responding at 12 and 24 months. These studies, then, demonstrate response to VNS increasing over months with response being reasonably well maintained in these difficult-to-treat depressed patients.

Very recently, Aaronson et al. [51] published a 5-year follow-up to their previous study comparing the effects of VNS or TAU in patients with TRD carried out for 50 weeks. This study has the longest duration of treatment so far. Consistent with their earlier results, the group receiving adjunctive VNS had better clinical outcomes than the group receiving TAU, with those receiving VNS having a significantly higher 5-year cumulative response rate (67.6% *vs* 40.9%) and a significantly higher remission rate (cumulative first-time remitters, 43.3% *vs* 25.7%) than those getting TAU.

A recent review by Cimpianu et al. [28] systematically reviewed the evidence for the efficacy of VNS in TRD, as well as other psychiatric disorders. For the other disorders, there were scant data and no conclusions could be made. The interested reader is directed to this comprehensive review, particularly Table 1, which gives details about the 33 studies included in their quantitative analysis, with 24 using standard VNS for TRD [as opposed to transcutaneous VNS (see below)]. As mentioned, the evidence from these in general nonrandomized open studies carried out over long time periods indicates benefit from VNS. This view is supported by a meta-analysis of 6 outpatient multicenter clinical trials of VNS + TAU or TAU alone, all of which were sponsored by Cyberonics, Inc., the manufacturer of the stimulation device. This analysis found that adjunctive VNS therapy was associated with greater response and remission than TAU alone, at time periods from 12 to 96 weeks [26]. Retrospective observational studies also support this view such as one involving Medicare patients [52] where patients with TRD receiving VNS had lower yearly medical costs postimplantation than those receiving TAU, and reduced annual mortality rates.

Nevertheless, it is wise to be cautious in the absence of more RCTs of the effectiveness of VNS in TRD before reaching definitive conclusions. This is likely why some national guidelines recommend VNS for TRD, whereas others are more circumspect (see [28]). But patients with TRD need help today. Given that VNS is generally well tolerated [12, 16, 49], together with the negative consequences of TRD, it should definitely be considered in the armamentarium of treatments for TRD.

A relatively new development may aid in its use for TRD. It has now been established that in humans the auricular branch of the vagus nerve is close to the surface in the ear, particularly the middle-third and lower-third area of the medial surface of the auricle [53]. This observation led to the use of ear clips to stimulate the vagus at this site. Furthermore, other auricular areas do not receive vagal innervation, such as the superior scapha, and this permits sham stimulation to be carried out, as well as actual stimulation. This noninvasive stimulation of the vagus nerve is referred to as transcutaneous VNS (tVNS). Such stimulation produces sensory evoked potentials recorded from the scalp [54], which provides a rationale that this technique could be used to affect brain function. Now, several studies have shown that short-term VNS generates fMRI blood oxygen level-dependent signal activations in limbic and brainstem areas [55, 56]. Furthermore, tVNS does cause changes in functional connectivity in brain in depressed patients, as measured using fMRI [57, 58]. In these latter studies, stimulation was carried out for 30 min twice each day for 5 days each week over 4 weeks. So as with the invasive VNS procedure, there is both an anatomic and functional rationale for studying effects of auricular stimulation of the vagus nerve for different types of brain disorders.

Two studies have assessed the efficacy of tVNS in patients with MDD; there is no indication that these patients were treatment resistant. In the first study [59], 37 patients received stimulation for 15 min either once or twice a day, 5 days weekly, for a rather short time interval (2 weeks). Stimulation parameters were adjusted such that the intensity was just below the threshold of perception, that is, when the stimulus was just noticeable. Sham stimulation consisted of using similar electrodes but having no current applied. Effectiveness was evaluated using both the patient-rated Beck Depression Inventory (BDI) and the physician-completed HAMD. In comparison with the effect of sham stimulation, significant improvement in depressive symptomatology was found using the BDI. However, this was not so for the HAMD, possibly because the sham stimulation had a greater effect on the HAMD than the BDI. Rong et al. [60] studied a total of 160 patients, with 91 receiving only tVNS for 12 weeks, whereas 69 initially received sham stimulation for 4 weeks followed by 8 weeks of tVNS. In this study, sham stimulation did consist of actual stimulation but at a place on the ear not receiving a distribution from the vagus nerve. Stimulation occurred for 30 min twice each day for 5 days

weekly, with the stimulation occurring at home. Stimulation intensity was adjusted to the highest point that the patients could tolerate. After 4 weeks of treatment, tVNS reduced HAMD scores significantly more than the reduction of those receiving sham stimulation and 27% of the patients were judged as responders after 4 weeks of tVNS, whereas no patient achieved response with sham stimulation. Further improvement continued at 8 and 12 weeks.

These preliminary results are promising, but obviously much more research needs to be carried out, not the least of which would be studies to determine the optimal frequency and duration to administer tVNS and whether it would be effective in patients with TRD.

Preclinical Studies

Before reviewing preclinical studies trying to ascertain the mechanism(s) of action of VNS, a brief overview of functional brain-imaging studies in humans treated with it is relevant as such research is helping to understand brain regions and circuits modulated by VNS either acutely or long term. A limitation of such studies, and indeed all clinical studies involving VNS, as mentioned later, is the fact that the study population remains on their drug regimen, which may involve multiple drugs, and can change during the course of the study. Blood cerebral flow, fMRI, and blood oxygen level-dependent fMRI reveal that acute VNS somewhat consistently causes changes in orbitofrontal, anterior cingulate, dorsolateral, prefrontal, and insular cortices, as well as the striatum, cerebellum, and brainstem [25, 61–64]. With regard to the chronic effects of VNS on brain regions, changes have been noted in the thalamus, prefrontal cortex (PFC), limbic system, hypothalamus, medulla, and cerebellum [62, 65–67], although there is some inconsistency with regard to the direction of the change caused by VNS.

As for tVNS in humans, Kraus et al. [56] studied healthy volunteers with electrical stimulation of the nerves in the left outer auditory canal. The brain areas activated by tVNS are consistent with those found with conventional VNS. In the same study, a control group receiving stimulation of the ear lobe instead of the left outer auditory canal showed no effect on limbic areas. Further, in patients with depression, the pattern of brain areas modulated by tVNS is also consistent with that obtained by conventional VNS [57, 68]. Recently, 4 weeks of VNS was found to alter the resting state functional connectivity between the right amygdala and left dorsolateral PFC as well as to enhance activation of the left insula, with such changes associated with improvement in depressive symptomatology [58, 69]. A more recent study using fMRI aimed to optimize activation of brain areas by tVNS by comparing 4 stimulation locations in the ear: the inner tragus, inferoposterior wall of the ear canal, cymba conchae, and earlobe (sham). Only stimulation of the cymba conchae produced a significantly stronger activation in both the NTS and LC than did the sham stimulation [70]. There have not yet been any studies evaluating such activation in improving depressive symptomatology.

Brain Areas Activated by VNS

Studies with animals are important to elucidate the mechanisms by which VNS produces its effects without confounds of having other drugs on board (as is the case in the clinic), as well as to optimize therapeutic stimulation parameters to increase further the number of patients with TRD achieving response and remission following VNS treatment. Acute, as well as chronic (sustained), activation of brain circuits following VNS treatment have been studied by conventional immunohistochemistry for c-fos or ΔFosB respectively [71–73]. Both c-fos and Δ FosB are expressed following neuronal activation. On the one hand, c-fos expression peaks within 1 to 3 h, being used as a marker of acute neuronal activation [74]. On the other hand, Δ FosB shows a time lag for its expression, but persists longer, so it is used as an indicator of sustained neuronal activation [75, 76].

Using nonanesthetized rats and stimulation parameters that do not cause cardiovascular activation, Cunningham et al. [71] reported that acute VNS treatment (2 h) induces c-fos expression in the NTS, paraventricular nucleus of the hypothalamus, PBN, BNST, and LC, but not in the cingulate cortex or DRN. VNS treatment for 2 weeks revealed significant increases in ΔFosB immunoreactivity in NTS, PBN, LC, peripeduncular nucleus, frontal cortex, cingulate cortex, hippocampus, basolateral amygdala, nucleus accumbens, BNST, and now the DRN [71, 72]. Results such as these show that VNS induces a rather complex pattern of activation of brain circuits implicated not exclusively in regulation of mood. That could perhaps expand the indications for the use of VNS (see [28]). In fact, some other clinical trials show some promise for the use of VNS for neurological diseases [77–79], ischemic stroke [80, 81], drug-seeking behavior [82], and trigeminal allodynia [83], amongst others.

Given the role of the vagus nerve in modulating the inflammatory reflex (see [84]), there has been a developing hypothesis that another putative mechanism by which VNS exerts its therapeutic effects in treating depression could be due to its role in decreasing proinflammatory cytokine synthesis [85, 86]. It is known that higher levels of proinflammatory cytokines are often measured in the serum or cerebrospinal fluid of depressed patients [87–89]. A small clinical trial [86] in patients with TRD showed that before VNS treatment such patients exhibited high levels of some proinflammatory cytokines. Three months following VNS treatment, an increased circulating level of anti-inflammatory cytokines was

measured in the same patients, corroborating the hypothesis that VNS modulates the immune system [86]. More recently another clinical trial showed that VNS inhibited proinflammatory cytokine production [90]; however, this study was not done in patients with TRD, but rather in patients with rheumatoid arthritis that had the disease attenuated by VNS [90]. More studies evaluating the role of VNS in reducing inflammation in patients with TRD are needed.

Effects on Biogenic Amine systems

It has long been hypothesized that the mechanism of action of conventional antidepressants is associated with enhancement in neurotransmission within the serotonergic and or noradrenergic systems [91–95]. So, electrophysiological recordings from noradrenergic neurons in the LC or serotonergic neurons in the DRN were performed to study, selectively, the activation of these cell types following acute and chronic VNS treatments. These were followed by microdialysis studies to measure extracellular norepinephrine (NE) and serotonin (5-HT) in different brain areas upon acute and chronic VNS treatment. Consistent with the immunohistochemical studies, electrophysiological recordings revealed that VNS acutely increases spontaneous firing activity in noradrenergic neurons in the LC [96], but not in serotonergic neurons in the DRN. This result is consistent with a recent brain-imaging study using positron emission tomography and the selective α_2 adrenergic receptor antagonist [^{11}C] yohimbine in anesthetized minipigs that showed that acute VNS decreased α_2 adrenergic receptor binding in limbic, thalamic, and cortical brain regions [97]. Only chronic (2 weeks) VNS treatment was able to enhance the firing rate of serotonergic neurons, and noradrenergic neurons in the LC remained activated by chronic treatment [96]. Lesion studies revealed that the chronic activation of serotonergic neurons in the DRN is downstream of VNS-induced activation of noradrenergic neurons in the LC. Moreover, the increased activity of the DRN neurons is mediated through activation of postsynaptic α_1 adrenoreceptors [96].

As shown by microdialysis, VNS rapidly increases NE levels in the cortex, medial PFC, amygdala, and hippocampus [98–100]. This is consistent with the rapid activation of NE neurons in the LC, which is upstream of these terminal regions. VNS-induced increases in extracellular NE in the PFC and hippocampus was also reported following chronic treatment [101]. Chronic, but not acute, VNS treatment was also found to cause an increase in 5-HT levels in the DRN, but not in the hippocampus [101].

The effect of VNS on the dopaminergic system shows some peculiarity. Manta et al. [101] found that in spite of dopamine (DA) cells in the ventral tegmental area (VTA) decreasing their firing rate in response to 2 weeks of VNS, extracellular DA levels in the PFC and nucleus accumbens were increased. Perez et al. [102] found that 2 weeks of VNS treatment in freely moving rats did not affect the number of spontaneously active DA cells in the VTA, nor their firing rate or burst firing [102]. By contrast, in the same study Perez et al. found that in a model where VTA cells were spontaneously active, namely the MAM model of schizophrenia [103, 104], chronic VNS normalized the activity within the VTA cells [102]. This might imply some utility of VNS in the treatment of schizophrenia. To date, there has only been one study such as this, using tVNS [105] of the outer ear canal. In this 26-week study, there was no significant improvement in schizophrenia symptomatology with tVNS *versus* sham tVNS.

Preclinical Behavioral Effects of VNS

The forced swim test (FST) has predictive validity for drugs or therapies that significantly improve depressive symptomatology in humans [106], whereas the NSFT is used to screen anxiolytic-like compounds or therapies [107]. Both acute and chronic VNS treatments decrease the time animals spend immobile in the FST, which is consistent with an antidepressant-like effect of VNS [71, 108, 109]. Chronic, but not acute treatment with VNS has an anxiolytic-like effect [108]. Lesioning either serotonergic or noradrenergic systems completely abolished the VNS-induced antidepressant and anxiolytic-like effects [108]. In the kainic acid rat model for temporal lobe epilepsy, Grimonprez et al. [110] found a decrease in saccharin preference, quite often associated with the human equivalent of anhedonia, a core symptom of depression. Such a decrease in saccharin preference was reversed upon VNS for 2 weeks. Such results support its clinical efficacy in patients with anhedonia.

Effect on Neurogenesis and Neurotrophins

The neurogenesis theory of depression is based on the findings that there is a stress-induced decrease in adult neurogenesis in the hippocampus, and that treatment with antidepressants reverse such deficit in neurogenesis [111–113]. Biggio et al. [114] examined the effects of acute (3 h) and chronic (1 month) VNS upon cell proliferation and found that the number of BrdU-positive cells in the dentate gyrus was significantly increased 24 h and 3 weeks after treatment. Another study by Revesz et al. [115] also showed that acute (48 h) VNS increased cell proliferation in the hippocampus. Another studied looking at the effects of chronic VNS on hippocampal neurogenesis in an animal model of depression, namely bulbectomy, revealed that the bulbectomy-induced decrease in neuronally differentiated BrdU-positive cells

within the dentate gyrus was prevented by VNS but not by sham stimulation [116].

Unlike positive results with acute VNS, acute treatment with traditional ADs does not increase neurogenesis; however, acute ECT, also used for TRD, does [117]. Antidepressants typically take 2 weeks to promote an enhancement in proliferation, but the outcome is rather variable [118–121]. Doublecortin (DCX) is a microtubule-associated protein used as a marker for neurogenesis, as it is expressed by neuronal precursor, as well as immature neurons, for about 2 weeks. Once they differentiate into mature neurons, they no longer express DCX [122, 123]. Both, acute and chronic VNS were associated with significantly higher expression of DCX in the dentate gyrus for up to 3 weeks after discontinuation of treatment [114]. Similar results were found after chronic treatment with fluoxetine [124]. This topic has been reviewed recently [125].

As with the neurogenesis theory, the neurotrophic theory of depression is based on findings that neurotrophic factor expression in brain circuits associated with mood regulation is inversely proportional to the effects of stress and antidepressants. One such neurotrophic factor widely studied in this framework is brain-derived neurotrophic factor (BDNF), along with its receptor, namely tropomyosin receptor kinase B (TrkB). From a functional perspective, the neurotrophic hypothesis is linked to the neurogenesis hypothesis as the increase in expression of neurotrophins with antidepressant treatment may block or reverse the neuronal loss associated with depression [126]. Chronic treatment (21 days) with classical antidepressants belonging to different classes increases expression of mRNAs for BDNF and trkB in the hippocampus (CA1, CA3, and dentate gyrus) [127, 128]. Acute (3 h) VNS treatment increases mRNA for BDNF in the hippocampus and cortex [98].

As reviewed by Shah et al. [33], drawing conclusions based on changes in mRNA for BDNF or protein levels can be complicated owing to factors such as translation, proteolytic cleavage, and release that are not accounted for. Hence, analyzing activation of its receptor, TrkB, may provide additional clues about the effect of antidepressant treatment on BDNF function. We have shown that both acute (2 h) and chronic (14 days) VNS activates the TrkB receptor, as shown by its causing phosphorylation at 3 tyrosine residues (Y705, Y816, and Y515) on TrkB [129]. Intraventricular pretreatment with a scavenger compound for TrkB, namely TrkB-Fc, which is a homodimer containing the extracellular ligand-binding domains of TrkB linked to human IgG1, prevented the acute VNS-induced increase in TrkB phosphorylation [130]. This suggests that VNS-induced activation of TrkB requires ligand to bind to it [130]. In contrast to the effects of VNS on the phosphorylation of TrkB, acute and chronic antidepressant treatments only cause phosphorylation at Y705 and Y816 but not at Y515 [129, 131, 132]. Y705 is the autophosphorylation site, whereas Y816 and Y515 are linked with the phospholipase C gamma 1 (PLCγ1) and MAPK/PI3K signaling pathways, respectively. Consistent with the phosphorylation of these tyrosine residues, acute VNS, as well as antidepressants, cause phosphorylation of PLCγ1 [133]; however, this is not maintained with chronic treatments. Only acute and chronic VNS, but not antidepressants, cause phosphorylation of ERK1/2 and Akt that are downstream of Y515 [129, 133]. A recent study by Shah et al. [130] show that intracerebroventricular pretreatment with K252a, an inhibitor of receptor tyrosine kinases, blocks the anxiolytic-like effect of VNS (2 weeks) in the NSFT. Intracerebroventricular pretreatment with K252a also blocked the acute effects of VNS in the FST. Such results indicate that the activation of TrkB by BDNF may be necessary for these behavioral effects of VNS.

As is so clinically, effects of noninvasive tVNS have not yet been intensively studied preclinically. In the Zucker diabetic fatty rat (fa/fa), in addition to the metabolic disarrangements a depressive-like phenotype is observed as seen by an increase in time spent immobile in the FST. Chronic (4 weeks), 30 min daily tVNS ameliorated the depressive-like phenotype [134]. In this study, 2 opposite magnetic electrodes were placed in the right auricular concha regions, inside and out for the cathode and anode, respectively. Finally, although not tVNS, it has been found that electroacunpunture of the auricular concha region, which is densely innervated by nerve endings from the vagus nerve, abolished the behavioral and neurochemical deficits caused by the unpredictable chronic mild stress paradigm [135]. Future studies regarding tVNS or electroacunpunture of the auricular concha regions in rodents need to be performed to evaluate which brain areas are being activated by such paradigms and the effects they produce in such areas, as has now been done for VNS.

In conclusion, VNS has been found to affect many of the same brain areas, neurotransmitters, and signal transduction mechanisms as altered by conventional antidepressants. More often than not, similarities have been found between preclinical effects of VNS and traditional antidepressants, although there are some exceptions [117, 133]. In spite of this, it is not clear what VNS is doing to allow it to be effective in patients when traditional antidepressants are not.

Further, the time course of clinical response to VNS with considerable improvement being noted between 3 to 12 months is quite different from the time course of drug-induced improvement of MDD, where optimal improvement often occurs in 8 to 12 weeks. This difference in the time course of clinical response might indicate some fundamental difference in the mechanisms of action of VNS, that is, indicating time-dependent effects not caused by traditional antidepressants. Another complexity in understanding effects of VNS is the absence of validated, widely used models for TRD, although some have been proposed [136–140]. Also,

animal studies are not carried out on the time scale where VNS is effective. Finally, animal studies have used VNS in the absence of other drugs on board. Yet this is not how VNS is used clinically where, as mentioned, it is added to TAU, which might involve multiple drugs and changing them. Whether there is some interaction between VNS and the effects of such drugs, in particular antidepressants, needs further study.

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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

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Objective: The Treatment-Resistant Depression Registry investigated whether adjunctive vagus nerve stimulation (VNS) with treatment as usual in depression has superior long-term outcomes compared with treatment as usual only.

Method: This 5-year, prospective, open-label, nonrandomized, observational registry study was conducted at 61 U.S. sites and included 795 patients who were experiencing a major depressive episode (unipolar or bipolar depression) of at least 2 years' duration or had three or more depressive episodes (including the current episode), and who had failed four or more depression treatments (including ECT). Patients with a history of psychosis or rapid-cycling bipolar disorder were excluded. The primary efficacy measure was response rate, defined as a decrease of ≥50% in baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score at any post-baseline visit during the 5-year study. Secondary efficacy measures included remission.

Results: Patients had chronic moderate to severe depression at baseline (the mean MADRS score was 29.3 [SD=6.9] for the treatment-as-usual group and 33.1 [SD=7.0] for the adjunctive VNS group). The registry results indicate that the adjunctive VNS group had better clinical outcomes than the treatment-as-usual group, including a significantly higher 5-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%). A subanalysis demonstrated that among patients with a history of response to ECT, those in the adjunctive VNS group had a significantly higher 5-year cumulative response rate than those in the treatment-as-usual group (71.3% compared with 56.9%). A similar significant response differential was observed among ECT nonresponders (59.6% compared with 34.1%).

Conclusions: This registry represents the longest and largest naturalistic study of efficacy outcomes in treatment-resistant depression, and it provides additional evidence that adjunctive VNS has enhanced antidepressant effects compared with treatment as usual in this severely ill patient population.

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Prospective serial depression treatment trials demonstrate that more than 60% of patients with major depressive disorder fail to remit with an initial pharmacotherapy trial, and a progressively smaller proportion of patients remit with each subsequent trial, until the remission rate after a fourth antidepressant trial is between 10% and 15% (1–4). Treatment-resistant depression refers to major depression that fails to remit after at least two separate and adequate trials of antidepressants from two different pharmacological classes. The Sequenced Treatment Alternatives to Relieve Depression trial (which did not include patients with bipolar disorders) showed that 32% to 41% of patients with treatment-resistant depression fail to remit after four trials of antidepressants, resulting in a large population of symptomatically and functionally impaired individuals (1, 5).

Vagus nerve stimulation (VNS) has been shown to be efficacious for the long-term management of patients with treatment-resistant depression (6, 7) and is approved by the U.S. Food and Drug Administration (FDA) as an adjunctive treatment for treatment-resistant depression. APA recommends VNS as a treatment option for patients who have not responded to at least four adequate trials of depression treatments, including ECT (8).

As a condition for approval of the treatment-resistant depression indication for VNS, the FDA required a post-marketing surveillance study, and therefore the Treatment-Resistant Depression Registry was established in 2006

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as a long-term, prospective, multicenter, open-label, nonrandomized, longitudinal, naturalistic, observational study to follow the clinical course and outcome over 5 years in two large cohorts of patients with treatment-resistant depression. Registry patients received either treatment as usual only (the treatment-as-usual arm) or treatment as usual with adjunctive VNS (the VNS arm), and the FDA agreed on a planned enrollment of 500 patients in the VNS arm and 300 patients in the treatment-as-usual arm. We hypothesized that the VNS arm would have superior clinical outcomes, based on long-term depression and mortality, compared with the treatment-as-usual arm. Here we report the 5-year findings from this registry, comparing treatment outcomes in the two groups, including response, remission, suicidality, and mortality, along with subanalyses of patients with a history of response or nonresponse to ECT, patients with comorbid generalized anxiety disorder, and patients with bipolar versus unipolar depression.

METHOD

The Treatment-Resistant Depression Registry

The registry included 61 sites in the United States representing academic, institutional, and private clinic settings that specialized in treatment of depression. The registry was approved by an institutional review board, and written informed consent was obtained from all study patients after the procedures had been fully explained. Registry data were collected between January 2006 and May 2015.

Patients were recruited by physician referral from all participating sites. They included patients who were being evaluated for surgery or anesthesia to undergo VNS implantation, patients who had signed surgical or anesthesia consent forms to receive a VNS device, patients who had a scheduled VNS implantation surgery, and patients who had completed participation in the VNS dose-finding study, referred to as the D-21 study (ClinicalTrials.gov identifier: NCT00305565).

Based on a study design in agreement with the FDA, the VNS arm in the registry included "new patients" (335 patients without prior VNS treatment) and "D-21 rollover patients" (159 patients who received VNS treatment in the D-21 study, which was being conducted simultaneously with the registry study; these patients rolled over into the registry after completing participation in D-21 as they fulfilled the registry's entry criteria) (9). Sensitivity analyses showed that there were no differences between the VNS arm (with or without the D-21 rollover patients) and the treatment-as-usual arm for any of the efficacy assessments (see the Supplemental Methods section of the data supplement that accompanies the online edition of this article). Therefore, in agreement with the FDA, the VNS pooled data were included in the registry data analyses.

For the D-21 rollover patients, the Clinical Global Impressions severity (CGI-S) score (10) from the D-21 screening visit was used to assess eligibility for enrollment in the registry. Data prior to VNS device implantation (baseline) and up to 1 year after implantation were included in the registry data set. Based on the time lapse from the original D-21 implantation surgery, D-21 rollover patients entered at the corresponding follow-up time point in the registry.

To be eligible for enrollment in the registry, patients had to be age 18 or older; have a current major depressive episode (according to DSM-IV-TR criteria and confirmed by the Mini International Neuropsychiatric Interview) (11) of ≥2 years in duration (unipolar or bipolar depression) or have a history of at least three depressive episodes including the current major depressive episode; and have a history of inadequate response to at least four depression treatments (including maintenance pharmacotherapy, defined as dosage per Physician's Desk Reference labeling for a minimum of 4 weeks, psychotherapy, and ECT). Diagnoses of psychiatric conditions were made by trained psychiatrists at each recruiting site. The following additional entry criteria were applicable prior to enrolling in either the registry or the D-21 study: a CGI-S score ≥4; no history of schizophrenia, schizoaffective disorder, any other psychotic disorder, or a current major depressive episode that included psychotic features; not currently psychotic; no history of rapid-cycling bipolar disorder; and no previous use of VNS (other than the D-21 rollover patients).

Before designating any enrolled patient as being lost to follow-up, the study site made at least two attempts to contact the patient (by either telephone or certified mail) and encouraged the patient to complete the exit form and perform a final follow-up visit.

Study Treatment and Outcome Measures

Prior to enrollment, registry patients (except for the D-21 rollover patients) were allowed to select the treatment arm of their choice; however, patients could also be assigned by the site to receive the alternate treatment for various reasons, including availability of surgical implantation at a site, number of allocated slots for implantation, availability of VNS devices that had been donated by the registry sponsor, or failure to qualify for insurance reimbursement for VNS implantation. The costs associated with device implantation surgery and related medical care during registry participation were covered by either the patient or the patient's health insurance policy.

Patients in the VNS arm underwent the implantation surgery before visit 2 (baseline). Postbaseline follow-up visits for all patients were scheduled to occur at 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months, at which data were collected on medical status, adjustment of mood disorder therapy (as needed in the judgment of the clinician), and concomitant treatments (there were no restrictions on concomitant treatments in this observational registry). The Montgomery-Åsberg Depression Rating Scale (MADRS) (12) (administered by central raters), the Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR) (13, 14), the CGI improvement (CGI-I) score, and the patient-rated Frequency, Intensity, and Burden of Side Effects Rating scale (15) were administered, and data were collected on mortality and suicidality (16).

After each patient visit, the site notified the central raters to initiate patient follow-up via telephone, which was conducted separately from the site visit. Central raters were unblinded nurses trained to assess suicidality. The central raters maintained continuous progress notes on each patient throughout the study and alerted investigators if any suicidal thoughts or actions had occurred or, in their opinion, might occur.

Suicidality was assessed on the basis of three measures: a score of 2 or 3 on QIDS-SR item 12 (corresponding to the responses "think of suicide or death several times a week for several minutes" to "have actually tried to take my life"), a response of "yes" to the question "Has the patient made a suicidal gesture or attempt since the last visit?" on the investigator-completed suicidality assessment, and a score ≥4 on MADRS item 10 (corresponding to the responses "probably better off dead" and "active preparations for suicide").

Analysis Populations and Statistical Analysis

The safety analysis population included patients in the treatment-as-usual arm who had completed the visit 2 (baseline) requirements and patients in the VNS arm who had undergone VNS device implantation before visit 2. The intent-to-treat population included patients who completed their baseline visit, received their respective treatment, and completed at least one postbaseline assessment.

All statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, N.C.). For inferential statistics and tests of hypotheses, analysis of variance models using PROC GLM in SAS were used for continuous variables for visit-wise comparisons of treatments. For modeling of nonlongitudinal categorical data, logistic regression models were used (PROC LOGISTIC) in SAS. The mixed-model repeated-measure models utilizing SAS PROC MIXED and/or generalized linear mixed model (PROC GLIMMIX) were fitted for longitudinal data involving repeated measures over time. Time-to-event analyses were summarized using Kaplan-Meier curves and Cox regression models. Log-rank testing was used to test the null hypothesis of equal event time distributions between treatment arms. Summary descriptive statistics were generated for continuous variables, and frequencies and percentages for categorical variables. Tests were two-sided, with a type I error rate of 5% at the 95% confidence level.

The propensity score method (17) was used to adjust for imbalance of baseline prognostic factors between treatment arms. The patient propensity scores derived from the modeling were stratified into quintiles, and the stratified quintiles variable was incorporated as a classification variable in the final models and hypothesis testing of treatment differences.

The primary efficacy endpoint was the percentage of responders in each treatment arm through 5 years of follow-up, with response defined as a reduction of ≥50% from baseline MADRS score at any postbaseline visit. Secondary efficacy endpoints included response based on a CGI-I score of 1 or 2 at a postbaseline visit and an improvement of ≥50% from baseline on the QIDS-SR; remission, based on a MADRS score ≤9 at a postbaseline visit, a QIDS-SR score ≤5 at a postbaseline visit, and a CGI-I score of 1 at a postbaseline visit; and duration of remission, based on time from first remission (MADRS score ≤9) to first recurrence (MADRS score ≥20). Safety endpoints, specifically suicidality, were analyzed using PROC GLIMMIX based on whether the risk was greater or less than it was at baseline, or unchanged.

There were no imputations of missing data. The use of mixed-model repeated-measure modeling was preferred because the application is simple and produces results similar to those of multiple imputations, and with the same assumptions (18, 19). Additional sensitivity analysis checks were conducted, including percentage of missing data that were found to be similar between the two treatment arms; a non-missing visit-wise analysis that showed the same trend as the primary mixed-model repeated-measure modeling results; and a tipping-point analysis to rule out missing-not-at-random bias, as opposed to missing at random (20, 21), which confirmed that there were no realistic deviations from missing-at-random assumptions, thus confirming the appropriateness of the primary analysis.

RESULTS

The safety analysis population included 795 patients—494 patients in the VNS arm (including 159 D-21 rollover patients) and 301 patients in the treatment-as-usual arm (see the Supplemental Results section of the online data supplement). A diagnosis of severe recurrent major depressive disorder was reported in 46% of patients in the VNS arm and 32% of patients in the treatment-as-usual arm (Table 1). About 27% (N=134) of patients in the VNS arm and about 24% (N=71) of patients in the treatment-as-usual arm had a primary diagnosis of bipolar I or bipolar II disorder. Other diagnoses and their frequencies are listed in Table 1.

At baseline, the mean number of failed treatments for depression was 8.2 (SD=3.3) in the VNS arm and 7.3 (SD=2.9) in the treatment-as-usual arm, and the mean lifetime number of attempted suicides was 1.8 (SD=4.0) in the VNS arm and 1.2 (SD=2.4) in the treatment-as-usual arm. The mean baseline MADRS scores for the two groups indicated moderate to severe depression. Overall, the patients enrolled in the VNS arm were more likely to have had ECT exposure, psychiatric hospitalizations, and suicide attempts, and they had higher mean depression rating scale scores, suggesting that they had more severe illness than those in the treatment-as-usual arm (Table 1).

Of the 494 patients in the VNS arm, 461 (93%), 289 (59%), 313 (63%), 334 (68%), and 300 (61%), respectively, completed years 1, 2, 3, 4, and 5 of the registry (the variable numbers in the VNS arm are due to D-21 patients who rolled over into the registry at various time points after implantation). Of the 301 patients in treatment-as-usual arm, 224 (74%), 185 (62%), 168 (56%), 149 (50%), and 138 (46%), respectively, completed years 1, 2, 3, 4, and 5 of the registry. Of the 358 patients (45%) who withdrew early, 195 were from the VNS arm (40%) and 163 were from the treatment-as-usual arm (54%). The

TABLE 1. Baseline Demographic Characteristics, Clinical Features, and Disposition of Patients With Treatment-Resistant Depression Receiving Treatment as Usual With or Without Adjunctive Vagus Nerve Stimulation (VNS) (Safety Population)

Characteristic or Measure	VNS Group (N=494)		Treatment-as-Usual Group (N=301)		p[a]
	N	%	N	%	
Female	350	71	211	70	0.810
Caucasian	478	97	274	91	0.006
Past treatment with ECT	280	57	120	40	<0.001
	Mean	SD	Mean	SD	
Age at baseline (years)	48.9	10.12	49.9	11.07	0.208
Age at initial onset of depression (years)	20.9	11.80	21.1	11.40	0.643
Age at initial diagnosis of depression (years)	28.9	10.79	29.5	11.89	0.410
Number of failed treatments for depression	8.2	3.3	7.3	2.9	0.010
Lifetime number of diagnosed depressive episodes	14.9	24.1	12.0	23.9	0.820
Psychiatric hospitalizations within 5 years before enrollment	3.0	4.6	1.9	4.7	<0.001
Lifetime suicide attempts	1.8	4.0	1.2	2.4	0.020
Baseline Montgomery-Åsberg Depression Rating Scale score	33.1	7.0	29.3	6.9	<0.001
Baseline Clinical Global Impressions severity score	5.2	0.8	4.7	0.7	<0.001
Baseline Quick Inventory of Depressive Symptomatology–Self Report score	18.2	4.6	15.7	4.9	<0.001
	N	%	N	%	
Primary diagnosis of current major depressive episode					
Moderate recurrent major depression	63	13	69	23	
Severe recurrent major depression	225	46	95	32	
Moderate single-episode major depression	16	3	30	10	
Severe single-episode major depression	56	11	36	12	
Bipolar I disorder, most recent depressive episode of moderate severity	25	5	21	7	
Bipolar I disorder, most recent depressive episode of severe severity	62	13	12	4	
Bipolar II disorder, most recent episode depressed	47	10	38	13	
Primary reasons for early study withdrawal					
Patient withdrew consent	55	11	37	12	
Patient nonadherence	40	8	39	13	
Patient did not meet the study eligibility criteria	3	0.6	1	0.3	
Participating physician's decision	4	0.8	7	2	
Death	7	1	8	3	
Other[b]	86	17	71	24	

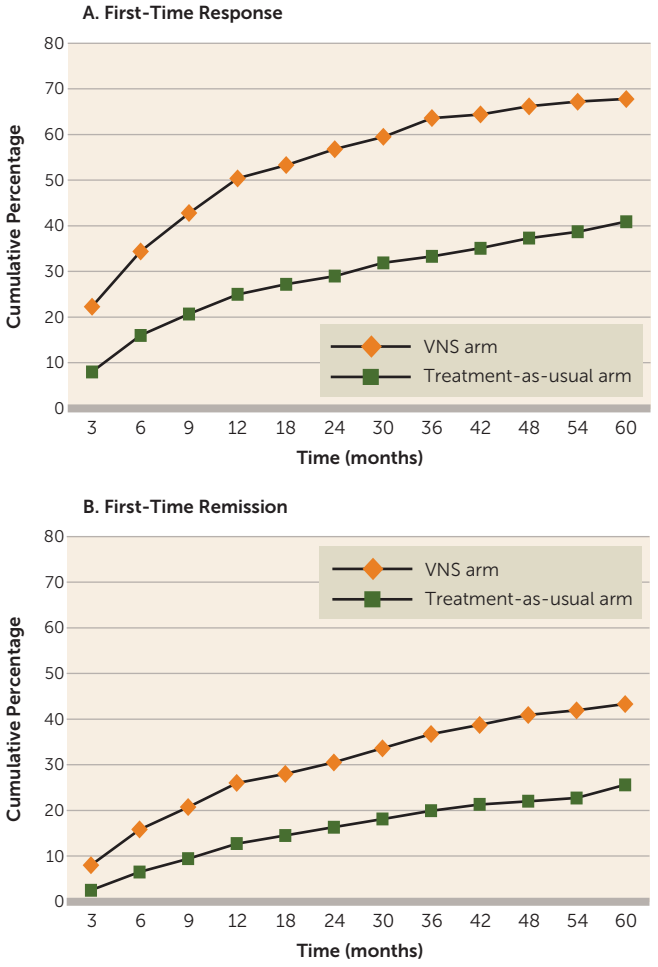
[a] After propensity score adjustment, all p values were >0.2.
[b] The other category includes patient choice to discontinue treatment, lost to follow-up, patient relocation, and site closure. After premature closure of a study site where 48 patients were participating in the treatment-as-usual arm, most of the patients at that site either were lost to follow-up or were dropped from the study because of nonadherence.

reasons for early withdrawal were similar between the treatment arms (Table 1).

A total of 765 patients (489 in the VNS arm and 276 in the treatment-as-usual arm) met the criteria for the intent-to-treat population and were included in the efficacy analyses.

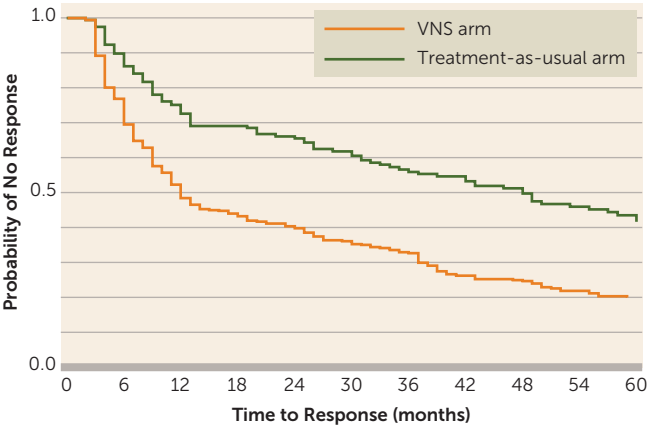
Patients could switch to the alternate treatment arm, and 22 patients elected to do so during the study; however, per protocol, data collected after a patient switched treatment arm were censored from the efficacy analysis.

FIGURE 1. Response and Remission Rates Among Patients With Treatment-Resistant Depression Receiving Treatment as Usual With or Without Adjunctive Vagus Nerve Stimulation (VNS)[a]



[a] The primary efficacy endpoint (panel A) was cumulative percentage of first-time responders over the 5-year follow-up period, with response defined as an improvement of ≥50% from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) score. A secondary efficacy endpoint (panel B) was cumulative percentage of first-time remitters over the 5-year follow-up period, with remission defined as a decrease to a score ≤9 on the MADRS at any postbaseline visit.

FIGURE 2. Kaplan-Meier Plot of Time to First Response Among Patients With Treatment-Resistant Depression Receiving Treatment as Usual With or Without Adjunctive Vagus Nerve Stimulation (VNS)[a]



[a] Response was defined as an improvement of ≥50% from baseline in Montgomery-Åsberg Depression Rating Scale score.

Primary Efficacy Evaluation of Response

A statistically significant difference was observed in the response rate between the VNS arm and the treatment-as-usual arm through the 5-year follow-up period (cumulative response rates, 67.6% [95% CI=63.4, 71.7] and 40.9% [95% CI=35.4, 47.1], respectively; p<0.001).

Figure 1A presents the cumulative percentage of first-time responders through the 5-year follow-up period, based on MADRS score. The cumulative percentage of first-time responders in the VNS arm was approximately double that in the treatment-as-usual arm at all postbaseline time points.

Secondary Efficacy Measures

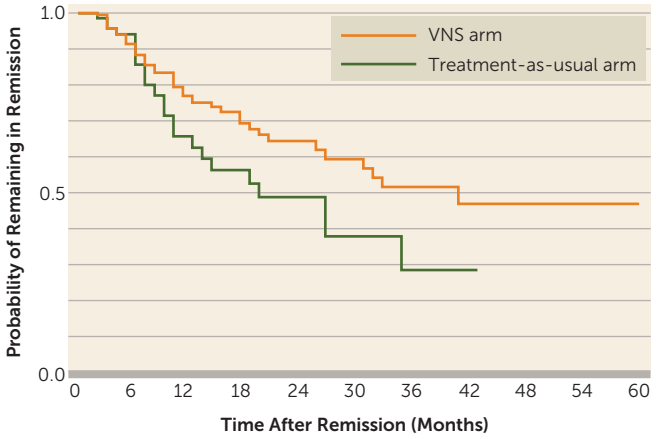
Response based on CGI-I and QIDS-SR. The proportion of responders for the 5-year follow-up data was also evaluated using CGI-I score (cumulative response rate, 75.9% [95% CI=72.3, 79.9] in the VNS arm and 48.6% [95% CI=43.0, 54.8] in the treatment-as-usual arm; p<0.001) and QIDS-SR score (cumulative response rate of, 64.7% [95% CI=60.7, 69.2] in the VNS arm and 41.7% [95% CI=35.9, 47.5] in the treatment-as-usual arm; p<0.001), and the results were consistent with the findings based on MADRS scores.

Remission. Figure 1B presents the cumulative percentage of first-time remitters through the 5-year follow-up period, based on MADRS score. Analysis of cumulative remission (based on a MADRS total score ≤9 at any postbaseline visit) demonstrated that over time, patients in the VNS arm were significantly more likely to experience remission than those in the treatment-as-usual arm (43.3% [95% CI=38.9, 47.7] and 25.7% [95% CI=20.7, 31.1], respectively; p<0.001). Based on QIDS-SR scores, there was a statistically significant difference in remission between the VNS and treatment-as-usual arms (40.4% [95% CI=36.2, 44.9] and 25.0% [95% CI=19.9, 30.1], respectively; p<0.001). Likewise, based on CGI-I scores, there was a statistically significant difference in remission between the VNS and treatment-as-usual arms (49.7% [95% CI=45.5, 54.3] and 21.4% [95% CI=16.7, 26.4], respectively; p<0.001).

Time to first response and duration of response. Figure 2 presents the Kaplan-Meier graph of time to first response for each treatment arm, based on MADRS scores. Median time to first response was significantly shorter for patients in the VNS arm than for those in the treatment-as-usual arm (12 months compared with 48 months; p<0.001).

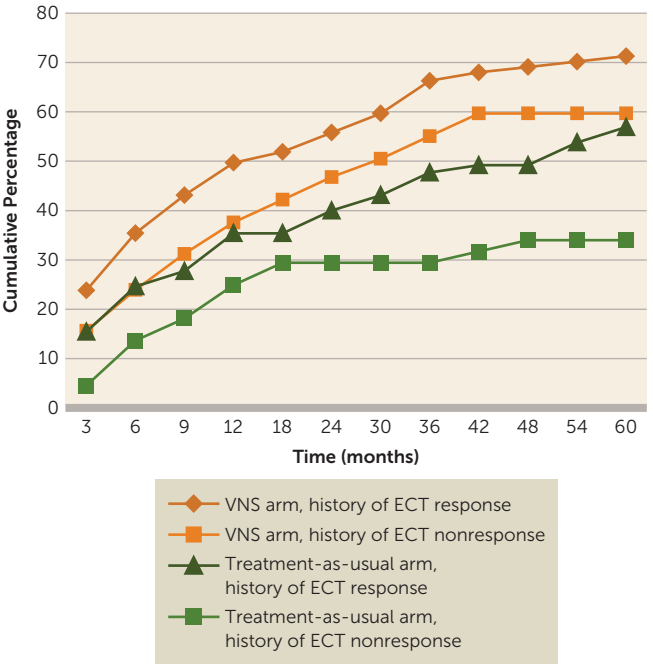
Response duration was assessed by fitting Kaplan-Meier curves of MADRS scores for each treatment arm. Patients in the VNS arm had a significantly longer median time to recurrence than patients in the treatment-as-usual arm (12 months compared with 7 months; p=0.001) (data not shown).

FIGURE 3. Kaplan-Meier Plot of Time to First Recurrence After Remission Among Patients With Treatment-Resistant Depression Receiving Treatment as Usual With or Without Adjunctive Vagus Nerve Stimulation (VNS)[a]



[a] Remission was defined as a decrease to a score ≤9 on the Montgomery-Åsberg Depression Rating Scale at any postbaseline visit, and recurrence was defined as an increase to a score ≥20 for the first time after achieving remission.

FIGURE 4. First-Time Response Among Patients With Treatment-Resistant Depression Receiving Treatment as Usual With or Without Adjunctive Vagus Nerve Stimulation (VNS): Subanalysis of Patients With a History of Response or Nonresponse to ECT[a]



[a] Response was defined as an improvement of ≥50% from baseline in Montgomery-Åsberg Depression Rating Scale score.

Time to first response and duration of response were also evaluated based on QIDS-SR scores. Median time to first response was significantly shorter for patients in the VNS arm than for those in the treatment-as-usual arm (22 months compared with 47 months; $p<0.001$). In addition, responders in the VNS arm had a longer median time to recurrence than did responders in the treatment-as-usual arm (10 months compared with 7 months), but this difference did not reach statistical significance ($p=0.14$).

Time to first remission and duration of remission. Summary analysis of the Kaplan-Meier time to first remission based on the MADRS data demonstrated that patients in the VNS arm had a significantly shorter median time to remission than patients in the treatment-as-usual arm (49 months compared with 65 months; $p<0.001$).

Figure 3 presents the median duration of remission (for those patients who remitted) with time to recurrence. The duration of remission based on the MADRS data was longer for patients in the VNS arm than for those in the treatment-as-usual arm (40 months compared with 19 months), but the difference did not reach statistical significance ($p=0.10$). Similarly, the duration of remission based on the QIDS-SR data was longer for patients in the VNS arm than for those in the treatment-as-usual arm (30 months compared with 18 months), but the difference did not reach statistical significance ($p=0.20$).

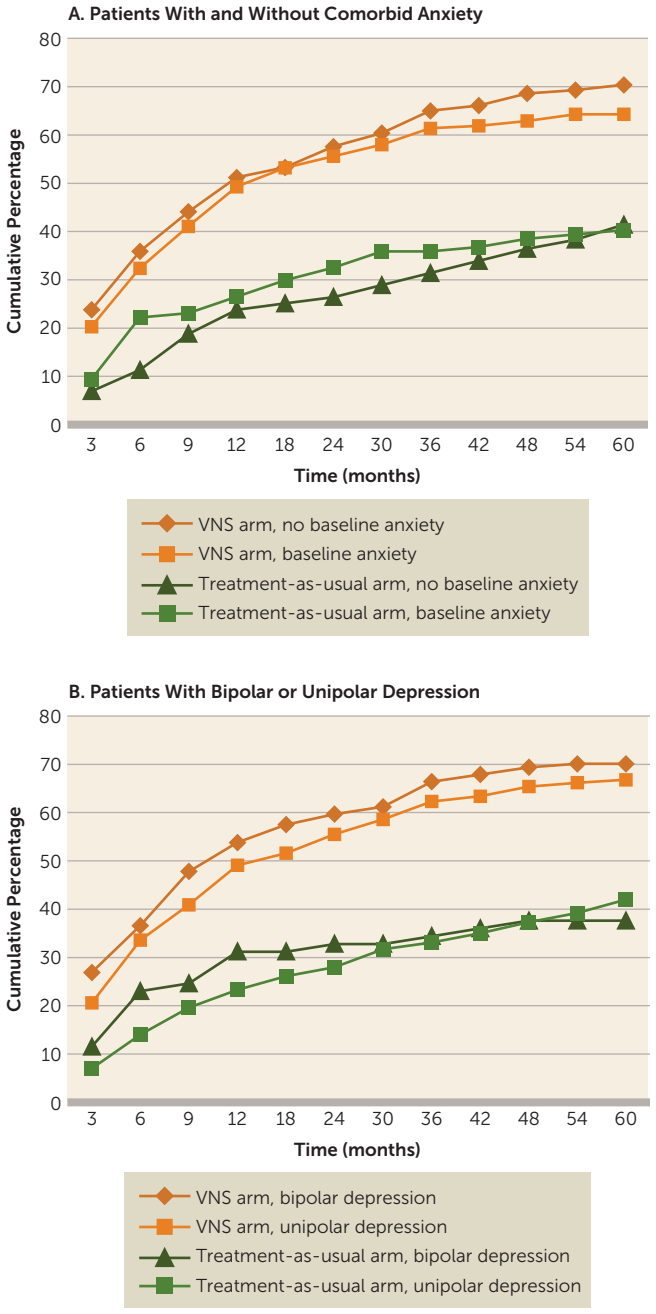
Subanalysis Based on Prior ECT Exposure, Comorbid Anxiety, and Bipolar Depression

A subanalysis was performed in registry patients who had previously completed one or more adequate courses of ECT (defined as at least seven right unilateral treatments). This subanalysis, which included 290 patients in the VNS arm (58.7%) and 109 patients in the treatment-as-usual arm (36.2%), compared cumulative response rates after grouping the patients by their history of response to ECT based on a review of medical records.

For patients included in this subanalysis, the cumulative percentage of first-time responders through the 5-year follow-up period based on MADRS score is presented in Figure 4. The 5-year cumulative response rate for patients in the VNS arm who had previously responded to ECT was 71.3% (95% CI=64.3, 77.4), compared with 56.9% (95% CI=44.8, 68.2) for the ECT responders in the treatment-as-usual arm, a statistically significant difference ($p=0.006$). In addition, a significant difference in response was seen at 9 months, and it was maintained for the duration of the study. For ECT nonresponders in the VNS arm, the response rate was 59.6% (95% CI=50.2, 68.4), compared with 34.1% (95% CI=21.8, 48.9) for ECT nonresponders in the treatment-as-usual arm ($p<0.001$), with statistically significant separation beginning after 2 years of treatment and continuing until completion of registry participation.

Subanalyses of cumulative percentage response rates were also performed for patients with and without a baseline presentation of comorbid generalized anxiety disorder (based on the Mini International Neuropsychiatric Interview) and patients with bipolar depression versus unipolar depression. Consistent with the findings based on the intent-to-treat population, the results of the subanalyses showed significant differences ($p<0.05$) within each comparator arm grouped by baseline comorbid anxiety or by unipolar

FIGURE 5. First-Time Response Among Patients With Treatment-Resistant Depression Receiving Treatment as Usual With or Without Adjunctive Vagus Nerve Stimulation (VNS): Subanalyses of Patients With or Without a Baseline Diagnosis of Comorbid Generalized Anxiety Disorder and Patients With Unipolar or Bipolar Depression[a]



[a] Response was defined as an improvement of ≥50% from baseline in Montgomery-Åsberg Depression Rating Scale score.

versus bipolar depression; the differences were evident by 12 months and continued to 60 months (Figure 5A and 5B).

Safety

Results based on the safety assessments of suicidality and mortality are presented below. Results related to frequency, intensity, and burden of side effects based on the patient-rated Frequency, Intensity, and Burden of Side Effects Rating scale are presented in the Supplemental Results section of the online data supplement. The safety profile based on this scale was similar between the two treatment arms, showing that adjunctive VNS does not lead to an additional side effect burden compared with treatment as usual only.

Suicide attempts and suicidal ideation. Based on three different outcome measures of suicidality (as outlined in the Method section), both treatment arms demonstrated an improvement from baseline over the course of study participation; however, the VNS arm showed a greater reduction in the suicidality profile compared with the treatment-as-usual arm. The difference was statistically significant for QIDS-SR item 12 (odds ratio=2.11, 95% CI=1.28, 3.48; p=0.035) and the investigator-completed suicidality assessment (odds ratio=2.04, 95% CI=1.08, 3.86; p=0.029), but not for MADRS item 10 (odds ratio=1.67, 95% CI=0.98, 2.83; p=0.058).

Mortality. All-cause mortality was markedly lower in the VNS arm than in the treatment-as-usual arm (3.53 per 1,000 person-years [95% CI=1.41, 7.27] and 8.63 per 1,000 person-years [95% CI=3.72, 17.01], respectively) (Table 2). The rate of completed suicides was also lower in the VNS arm than in the treatment-as-usual arm (1.01 per 1,000 person-years [95% CI=0.11, 3.64] and 2.20 per 1,000 person-years [95% CI=0.24, 7.79], respectively).

Fifteen patients died during the study, including seven in the VNS arm and eight in the treatment-as-usual arm. Information on deaths and related causes is provided in the Supplemental Results section of the online data supplement.

DISCUSSION

Findings from this long-term, naturalistic, prospective, longitudinal, multicenter, open-label, observational patient outcome registry study provide important outcome information about a patient population that is not generally studied. These were patients who continued to experience severe and chronic depression after an average of 8.2 failed treatments for depression.

As demonstrated in this study, patients in the VNS arm experienced clinically and statistically significant benefits compared with patients in the treatment-as-usual arm for most of the measured clinical efficacy outcomes. Although the indices of depressive severity at baseline suggest that patients in the VNS arm were a more severely ill group than those in the treatment-as-usual arm, the patients in the VNS arm had significantly more positive outcomes in response rate, time to response, and duration of response, while also experiencing reduced mortality and suicidality, as evident in both the clinician-rated and the patient-rated scales.

The improved outcomes with adjunctive VNS observed for both ECT responders and nonresponders is remarkable. For patients who respond to ECT–who often rely on

maintenance ECT or additional courses of life-disrupting treatment with ECT–VNS may provide a tolerable alternative, and for patients who do not respond to ECT–for whom psychiatric care offers limited therapeutic options–VNS demonstrates significant efficacy.

As there is a lack of evidence-based biological treatment options for treatment-resistant depression (other than ECT), the results from this registry provide encouragement to pursue aggressive neurostimulation interventions.

There are several important limitations to our registry design. Given ethical concerns about following such a severely ill patient population over a 5-year period, the registry had a naturalistic, observational design and did not randomly assign patients to the treatment groups (22, 23). Similarly, the treatment assignment in the registry was not blinded, in part because it would have been unethical to implant a sham device for a long duration in severely ill patients.

A robust treatment response was observed in the VNS arm, exceeding the response rate in the treatment-as-usual arm, and it is reasonable to ask whether this represents an effect in which patients have a higher expectation of therapeutic improvement with an implanted device (24). While not exactly equivalent to an expectation effect, a potential for a "placebo" effect is diminished by the patients' elevated baseline illness severity and chronicity (25). It would also seem unlikely that an expectation effect would endure over several years, but this has not been studied in a trial of this duration. Also, in the ECT subanalysis, separation between groups only begins at 9 months for the responders and at 2 years for the nonresponders. It seems unlikely that an expectation effect would commence after so much time had elapsed.

Inclusion of the D-21 rollover patients in the VNS arm may be another study limitation, as the D-21 rollover patients who had a positive experience with VNS may have been more likely to participate in the registry; however, a sensitivity analysis of the VNS group (with and without the D-21 rollover patients) demonstrated similar treatment effects and similar treatment differences in comparison to the treatment-as-usual arm.

The 1-year response and remission rates in the treatment-as-usual arm were considerably higher compared with those in a study by Dunner et al. (22) that examined the effects of treatment as usual in patients with treatment-resistant depression. Among the registry patients in the treatment-as-usual arm, the rates after 1 year of treatment were 25% for response and 12% for remission, compared with 12% and 4%, respectively, in the Dunner et al. study. It is not clear what factors contributed to the higher response and remission rates in the registry study, but it is possible that differences in baseline illness status or the frequency of visits in the registry study contributed to improved response and remission rates in the treatment-as-usual arm.

In summary, adjunctive VNS resulted in superior outcomes in both effectiveness and mortality over a 5-year period compared with treatment as usual alone for patients with a chronic, severe course of treatment-resistant depression, a patient population for whom evidence-based treatment options do not currently exist.

TABLE 2. Analysis of Suicidality and Mortality Among Patients With Treatment-Resistant Depression Receiving Treatment as Usual With or Without Adjunctive Vagus Nerve Stimulation (VNS) (Safety Population)

Measure	VNS Group (N=494)	Treatment-as-Usual Group (N=301)
Number of deaths during study participation	7	8
Exposure (patient-years)	1,985.08	926.49
All-cause mortality per 1,000 person-years	3.53	8.63
Number of suicides during study participation	2	2
Suicides per 1,000 person-years	1.01	2.20

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Patient Perspective

"Ms. A" was a 35-year-old divorced noncustodial mother of one child at the time of study entry. She was suffering from treatment-resistant bipolar depression and exhibited poor functioning. She had a long and complex medical history of multiple hospitalizations (mostly for depression), had made two suicide attempts by medication overdose, had unsuccessfully tried 12 different antidepressants, and had experienced several changes from depressed states to mixed states in response to various antidepressants. At the time Ms. A entered the VNS study, she had been in the current depressive episode for more than 2 years. She described feeling "like being dead with your eyes open." Ten months after being in the VNS study, Ms. A attempted suicide and was subsequently hospitalized. Most of her medications were discontinued, including oxcarbazepine and valproate, and she continued to receive only quetiapine (at dosages ranging from 200 to 500 mg/day) and adjunctive VNS. She received this treatment regimen for the remainder of her study participation, as well as afterwards, for a total of 9 years (with a VNS device battery change at the 8-year mark). At one point, she stopped taking quetiapine and was hospitalized for mania, but she has felt well since resuming its use.

Ms. A has an active social life, and her child has lived with her for the past 6 years. She has stated, "I would not be here if not for the device.… I have a sense of hope and confidence that I never have to feel as bad as I did."

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MINI REVIEW
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Vagus Nerve Stimulation (VNS) and Other Augmentation Strategies for Therapy-Resistant Depression (TRD): Review of the Evidence and Clinical Advice for Use

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In addition to electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS) is one of the approved neurostimulation tools for treatment of major depression. VNS is particularly used in therapy-resistant depression (TRD) and exhibits antidepressive and augmentative effects. In long-term treatment, up to two-thirds of patients respond. This mini-review provides a comprehensive overview of augmentation pharmacotherapy and neurostimulation-based treatment strategies, with a special focus on VNS in TRD, and provides practical clinical advice for how to select TRD patients for add-on neurostimulation treatment strategies.

Keywords: vagus nerve stimulation, therapy-resistant depression, neurostimulation, clinical practice, affective disorders

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INTRODUCTION

Major depressive disease (MDD) is recognized worldwide as a frequently recurring or chronic and highly prevalent psychiatric disease (Beaucage et al., 2009; Maske et al., 2015). In addition to alterations in the typical domains of affective and mood symptoms, MDD is directly associated with high rates of suicidality and overall mortality as well as a well-established increased risk of death due to comorbid somatic disorders, such as myocardial infarction and stroke (Lasserre et al., 2017; Slepecky et al., 2017; Tesio et al., 2017; Vandeleur et al., 2017). Therefore, it has been projected that MDD will be the second leading cause of disability worldwide by the year 2020 (Michaud et al., 2001; Effinger and Stewart, 2012; Manetti et al., 2014). In addition to psychotherapeutic strategies, pharmacotherapy is usually used as a first-line treatment for MDD, yet many patients do not sufficiently respond to monotherapy with an established medication, such as a selective serotonin reuptake inhibitor (SSRI) (Fava and Davidson, 1996). Some progress has been made in developing safe and efficacious antidepressant treatments and novel pharmacotherapy-based treatment strategies, such as ketamine or selective NMDA receptor subtype 2B (NR2B) antagonists (Serafini et al., 2015; Andrade, 2017) with mechanisms other than monoamine neurotransmitter reuptake inhibition. Ketamine was found to quickly reduce depressive symptoms within hours of a single administration, thus further demonstrating the important role of glutamate in the development of depression (Serafini et al., 2014). However, data on the remission and recurrence rates of

TRD under ketamine are still lacking. In summary, there currently seem to be no fundamental emerging innovations for the long-term treatment of MDD with antidepressant pharmacotherapy. Supportive, noninvasive add-on strategies, such as light-based therapy and exercise as well as alternative strategies, such as acupuncture and yoga, are used alongside pharmacological treatment strategies; however, their status within current treatment regimens is yet to be established, and many strategies are difficult to apply in an outpatient setting. Although evidence-based psychosocial interventions (Hunot et al., 2013; Hayes and Hofmann, 2017) are also under development, unfortunately, up to 50% of all patients with MDD do not achieve remission with currently available treatments (Zhou et al., 2015; Murphy et al., 2017). This subtype of MDD is classified as therapy-resistant depression (TRD) (Rush et al., 2006a,b; Mojtabai, 2017), which is defined by a lack of response or failure to fully respond or achieve remission after trials of at least two proven antidepressants with adequate dosing and duration (Bschor, 2010; Wiles et al., 2014; Holtzmann et al., 2016). At least one-third of all MDD patients are considered "therapy-resistant" (Rush et al., 2006a,b) (ongoing controversy discussed). Therefore, TRD disproportionally accounts for the largest proportion of the disease, underscoring the importance of innovative add-on therapy strategies for this particular type of TRD (McCullough, 2003; "Yoga for anxiety...", 2009; Rizzo et al., 2011; Oldham and Ciraulo, 2014; Lucas et al., 2017; Sakurai et al., 2017).

Add-on or augmentation therapy means the combination of first-line antidepressive pharmacotherapy with a second treatment approach. In addition to pharmacological add-on therapy, neurostimulation techniques are increasingly used. Today, the most promising neurostimulation tools used to treat TRD are (1) Electroconvulsive therapy (ECT), (2) Transcranial direct current stimulation (tDCS), (3) Repetitive transcranial magnetic stimulation (rTMS), (4) Deep brain stimulation (DBS), (5) Magnetic seizure therapy (MST), (6) Cranial electrotherapy stimulation (CES), and (7) Vagus nerve stimulation (VNS). Each has a different application procedure, and there is a large variation in their effects and the clinical expertise required.

This mini-review provides a comprehensive overview of neurostimulation-based treatment strategies with a special focus on VNS in TRD and finally, aims to provide practical clinical advice for their use when selecting TRD patients for add-on neurostimulation treatment strategies.

ADJUNCTIVE BIOLOGICAL OPTIONS FOR TREATING TRD ALONGSIDE ANTIDEPRESSANT PHARMACOTHERAPY

Augmentation Pharmacotherapy

Lithium

Lithium augmentation is (still) the state-of-the-art treatment in add-on and augmentative therapy with antidepressants when facing the challenge of TRD. Solid evidence from both large open-label and placebo-controlled trials highlights its efficacy in the treatment of resistant depression (Stage et al., 2007; Young, 2013; Nelson et al., 2014). Its notable effects include regulation of mood and circadian rhythms, and it also has a positive effect on suicidality and overall mortality. Lithium augmentation has significantly better antidepressant effects than the placebo, with a mean response rate of 41.2% (vs. 14.4%). Nevertheless, the risk of side effects (e.g., metabolic, cardiovascular, nephrologic) is significant, and its toxicity, especially when inadequate doses limit the clinical use of lithium, is notable (Edwards et al., 2013, 2014; Nelson et al., 2014; Hincapie-Castillo and Daniels, 2017).

Atypical Antipsychotics

Atypical antipsychotics comprise the most-studied class of augmenting agents for SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) for depression (Kato and Chang, 2013; Fornaro et al., 2016; Bartoli et al., 2017). The FDA has approved both quetiapine and aripiprazole as well as the combination of olanzapine with fluoxetine for augmentation. Other agents include ziprasidone and risperidone, which have also been shown to be effective in treating MDD/TRD (Gabriel, 2013; Nelson, 2015).

Patients treated with atypical antipsychotics are approximately twice as likely to reach remission as patients treated with the placebo, as highlighted in several studies (De Fruyt et al., 2012; Spielmans et al., 2013; Wright et al., 2013; Fornaro et al., 2016). The use of atypical antipsychotics involves a careful risk-benefit assessment because these agents possess serious short- and long-term treatment-emergent (potentiated through combination therapies) side effects (e.g., sedation, central obesity, metabolic syndrome, and extrapyramidal side effects) (Shirzadi and Ghaemi, 2006; Fraguas et al., 2008; Temmingh, 2012; Sykes et al., 2017).

Thyroid Augmentation

Thyroid hormones are an additional established option for the adjunctive treatment of TRD. Specifically, triiodothyronine (*T3*) is preferred for augmenting antidepressants due to its bioactivity in the CNS. In a meta-analysis of *T3* augmentation (25–50 μg/day) in probands who failed to respond to tricyclics, Aronson and colleagues found that *T3*-treated patients were twice as likely to respond as placebo-treated-patients (Aronson et al., 1996). In STAR*D, *T3* augmentation resulted in a 24.7% remission rate compared with a 15.9% remission rate for lithium augmentation in treatment-resistant patients who failed two previous antidepressant trials (Nierenberg et al., 2008; Warden et al., 2009). A disadvantage of T3 medication is its interference with thyroid metabolism in patients without hypothyroidism. Thus, treatment should be restricted to a few weeks, making this option unsuitable as a maintenance treatment (Cadieux, 1998).

Additional Agents Used for Pharmacologic Augmentation

A number of further drugs of diverse neuropsychopharmacological classes and properties are used as augmentation strategies of first-line antidepressive treatment for TRD. These drugs, which include bupropion, buspirone, methylphenidate, dopamine agonists, anticonvulsants, mirtazapine, modafinil, and pindolol (Dording, 2000), have been shown to possibly add to the antidepressive effect of

first-line antidepressive treatment for TRD when administered in combination therapy. However, the scientific evidence for most of these agents is still comparably limited. In a recent meta-analysis of pharmacological augmentation strategies (Zhou et al., 2015), bupropion, buspirone, lamotrigine, methylphenidate, and pindolol all failed to show a superior effect compared to placebo.

Neurostimulation Options

Some promising neurostimulation tools for TRD in addition to VNS are described below.

ECT and rTMS (which has lower effect sizes) still stand as the gold standards for treatment with level I evidence (Pagnin et al., 2004; Minichino et al., 2012; Berlim et al., 2013b). MST and tDCS seem to be an option, especially when serious side effects occur during treatment with ECT. For DBS, the data are still limited due to small study groups, but the available data and experiences are promising.

Electroconvulsive Therapy (ECT)

ECT is the oldest neurostimulation therapy for treating TRD. It has been widely used in large-scale clinical studies of depression and has been found to be more effective than antidepressant drug use alone. It is also the most common therapeutic option for severe and recurrent depression when medication and psychotherapy have been unsuccessful (Kellner et al., 2012; Berlim et al., 2013b; Kellner, 2014). Based on solid data from six trials, a meta-analysis concluded that real ECT is significantly more effective than simulated (sham) ECT (standardized effect size 0.91, 95% CI −1.27 to −0.54) (The UK ECT Review Group, 2003).

Patients are given general anesthesia and a muscle relaxant before ECT and are continuously monitored throughout the procedure. Then, an electric current used to stimulate cerebral brain regions induces a generalized central seizure. The electrode placement is relevant to both efficacy and the development of side effects. The symmetric bitemporal electrode placement, which covers a large brain volume and induces a high level of seizure generalization, has high efficacy but produces more side effects than other placements. Unilateral ECT, in which the electrodes are placed on the right temple and to the right of the vertex, lowers the seizure generalization, efficacy and side effects (Calev et al., 1995; Prudic, 2008; Sidhom and Youssef, 2014; Muller et al., 2017b).

In clinical practice, the acute ECT treatment phase typically comprising 3 treatments/week can be followed by a taper phase with a reduction to 1–2x/week and then to 1x/week for several weeks. Many patients will then receive further maintenance ECT with a single treatment every 3–6 weeks. Importantly, there is no evidence for a need to limit the lifetime number of treatments in patients who need ongoing treatment (Kellner et al., 2012).

Overall, it can be concluded that ECT is a valid therapy for the treatment of TRD, including its severe and resistant forms. After remission, ECT is often replaced with maintenance ECT (mECT) to prevent relapse. However, good clinical outcomes, are diminished through high relapse rates of up to 50%" (Rifkin, 1988; Kho et al., 2003; Charlson et al., 2012; Pinna et al., 2016). Therefore, there is a 57% relapse rate with optimized pharmacotherapy and a 65% rate after a successful ECT series. The relapse rate remains 37% despite optimized pharmacotherapy and lavish and costly mECT sessions (Kellner et al., 2006; Eschweiler et al., 2007; Post et al., 2015).

Magnetic Seizure Therapy (MST)

MST is a non-invasive convulsive neurostimulation therapy that induces an electric field in the brain and elicits a generalized tonic-clonic seizure. MST is being investigated as an alternative to ECT for use under general anesthesia with assisted ventilation and continuous electroencephalographic (EEG) monitoring. MST has the potential for fewer side effects, such as cognitive dysfunction, than ECT (Lisanby et al., 2003; Allan and Ebmeier, 2011), but optimal stimulation parameters for MST are still being investigated. Most studies have used a coil placed at the vertex with a frequency of stimulation of 100 Hz, a pulse width of 0.2–0.4 ms, and a stimulation duration of 10 s (Kito, 2017). There are no large-scale studies comparing MST to sham stimulation and no large-scale controlled studies of relapse following maintenance MST (mMST) with regard to prevention strategies, so the therapy is still in the experimental stage (Allan and Ebmeier, 2011).

Transcranial Direct Current Stimulation (tDCS)

In tDCS, cortical areas are stimulated non-invasively via a low-intensity direct current. Stimulation via sponge-based rectangular pads lasts for 10–20 min and modulates the neuronal excitability in target cerebral regions (Tschirdewahn et al., 2015; Palm et al., 2016b). The stimulation is focused on the left dorsolateral prefrontal cortex region (DLPFC) to minimize hypo-activity of the left DLPFC, which is a main target region in depression (Berlim et al., 2013a; Dell'Osso and Altamura, 2014; Meron et al., 2015). This therapy has almost no side effects and is well tolerated among all treatment groups. Stimulation of cortical regions may result in changes in membrane resting potentials and modify synaptic transmission in the DLPFC, which ultimately results in a significant, but only moderate, reduction of depression (Liebetanz et al., 2006; Palm et al., 2016a).

Repetitive Transcranial Magnetic Stimulation (rTMS)

Clinically used since the mid-80s, rTMS delivers external magnetic pulses to the cortex. These pulses induce an electrical potential in the brain tissue that depolarizes target neurons (Bulteau et al., 2017; McClintock et al., 2018). Stimulation can be high frequency (1 Hz) or low frequency (<1 Hz), and rTMS can also be used in the form of maintenance rTMS (mrTMS) (Rachid, 2018). Low-frequency rTMS inhibits certain cortical regions, whereas high-frequency rTMS activates the stimulated regions (Baeken et al., 2009; Bakker et al., 2015). It has been used to reduce depression, even in patients with medication-resistant major depression, with very few side effects and up to a 60% response rate, but has only a small antidepressant effect during follow-up after short and acute treatment in the absence of active maintenance treatment (Dell'osso et al., 2011; Kedzior et al., 2015). Similarly, rTMS response rates are poor

in patients for whom ECT has failed (Kedzior et al., 2017). These findings indicate that rTMS should be considered prior to pursuing ECT or as an add-on strategy and that patients who have not responded to ECT are unlikely to respond to rTMS treatment sessions alone (McClintock et al., 2018). The side effects of rTMS are mild and of short duration. Therefore, rTMS is a therapy that can be used for common depression treatment and is beneficial when combined with other standard treatments, such as pharmacotherapy and/or psychotherapy and other neurostimulation options (Perera et al., 2016). In recent years, there has also been growing evidence that, in addition to improvement of mood, rTMS might have a positive effect on cognitive functioning, which is often significantly reduced in patients with major depression. Aspects of cognitive performance reported to improve under rTMS include verbal memory, executive functioning, visuospatial ability, and recognition of facial expressions (Demirtas-Tatlidede et al., 2013). This may be an important advantage of rTMS, since cognitive impairment in MDD is insufficiently targeted by many other treatment options.

Deep Brain Stimulation (DBS)

DBS is an invasive neurosurgical procedure for TRD. The targeted approach involves stereotaxic placement of unilateral and/or bilateral electrodes in predefined brain regions. These electrodes are then connected to an implanted neurostimulator. Although the mode of action remains unclear, it is hypothesized that chronic, high-frequency stimulation (130–185 Hz) reduces cerebral neural transmission by inactivating voltage-dependent ion channels and clinically restores the activity of specific neuronal circuits involved in TRD ("Deep brain stimulation...", 2010; Cusin and Dougherty, 2012; Berlim et al., 2014). The targeted regions include the inferior thalamic peduncle, nucleus accumbens, lateral habenula, ventral striatum and subgenual cingulate cortex. Depending on the regions of interest, DBS is supposed to have antidepressant, strong antianhedonic, and antianxiety effects in TRD patients. It results in improvements related to social functioning, physical health and mood and anhedonic symptoms within TRD (Buhmann et al., 2017). No significant adverse effects of DBS (when implanted) have been recorded, thus highlighting DBS as promising in serious and chronic TRD. However, at this time only few clinical data sets with small sample sizes are available because the procedure is complex and requires direct brain surgery (Schlaepfer and Lieb, 2005; Kennedy et al., 2011; Jiménez et al., 2013; Lozano and Lipsman, 2013).

Cranial Electrotherapy Stimulation (CES)

In pulsed CES, low-amplitude electric currents (<1 mA) are broadly applied to the brain via scalp electrodes. CES has been approved for the treatment of anxiety, depression, and insomnia by the FDA (Gilula and Barach, 2004; Gunther and Phillips, 2010; Kavirajan et al., 2014). CES may affect the reticular activating system, the limbic system, and the hypothalamus (Kirsch and Nichols, 2013). How CES exerts its antidepressant effect is not fully understood. A recent study showed that CES could deactivate cortical brain activity and alter connectivity in the default-mode network (Kavirajan et al., 2014). Clinically, CES also seems to decrease comorbid depression in anxiety disorders (Feusner et al., 2012; Kirsch et al., 2014). However, a Cochrane library review indicates that methodologically rigorous studies of the antidepressant effects of CES in the treatment of acute depression are still lacking (Kavirajan et al., 2014). How CES modulates underlying neuroplasticity or signaling pathways also needs clarification.

Vagus Nerve Stimulation (VNS)

After decades of animal experimentation and application and after significant reductions in the frequency and severity of seizures were observed in response to stimulation of the vagus nerve, VNS was first applied in a human case of refractory epilepsy in 1988 (Rutecki, 1990; Uthman et al., 1990). VNS was then commercially approved for treatment of resistant epilepsy in 1997 (McLachlan, 1997; DeGiorgio et al., 2000; Henry, 2002). After showing its remarkable antidepressive clinical mode of action in a spin-off study and other controlled studies of TRD, it received approval for TRD in Europe and Canada in 2001–2005 (Sackeim et al., 2001; Topfer and Hailey, 2001; Marangell et al., 2002; Kosel and Schlaepfer, 2003). The therapy was then approved by the FDA for chronic depression and TRD in patients aged 18 years or older who do not respond to other antidepressant treatments (Nahas et al., 2006). Over 100,000 patients/year (both neurological and psychiatric indications) are treated worldwide (Cusin and Dougherty, 2012).

Surgical implantation is achieved by means of minor surgery, mainly neurosurgical, or otolaryngologic (Ng et al., 2010; Elliott et al., 2011).VNS requires an implantable pulse generator, which is surgically inserted under the skin of the chest and connected to an electrode placed in one of the vagus fibers in the neck. The repeatedly stimulated vagus nerve sends impulses from the periphery, where the electrode is placed, to the brain. Electrical stimulation of the vagus nerve centrally stimulates the nucleus tractus solitarius, which in turn is able to modulate multiple regions of the brain via its neuronal connections to anatomically distributed cortical and subcortical regions of the brain, the raphe nuclei and locus coeruleus, especially the limbic system. The right vagus nerve is not used because of the risk of potential severe bradycardia or arrhythmias. The left vagus nerve, whose fibers point to the central region, is used in VNS, which mainly stimulates the afferent fibers that communicate with the target regions to achieve improvement in mood. Therefore, this location is responsible for one of the main clinical effects of VNS.

In its mode of action, VNS modulates the concentrations of neurotransmitters (especially serotonin, norepinephrine, GABA and glutamate) and their metabolites while producing changes in the functional activity of CNS regions, which makes the mode of action of VNS similar to that of most antidepressants. Neuroimaging studies have shown evidence that activity in the thalamus and cortex in depressed patients is altered by VNS therapy. Changed activity in the orbital and ventromedial prefrontal cortices has also been recorded (Chae et al., 2003; Muller et al., 2013b). The most frequent acute complications of VNS implantation include temporary salivation, coughing, paralysis of the vocal cords, lower facial weakness, rarely

TABLE 1 | Neurostimulation options for treatment of TRD.

Technique	Main stimulation target region	Mode of action	Evidence	Pro	Con
ECT	Cerebral cortex	Small currents and generalized seizure induction	Strong	First line therapy for patients who failed in pharmacotherapy, rapid antidepressive effects, long-lasting clinical experiences	Relapse rates, effort, cognitive side effects
tDCS	Cerebral cortex	Anode and cathode sending constant low current (0.5–2 mA) directly to the brain	Weak-moderate	Non-invasive, rapid effects	Less clinical experience
rTMS	Cerebral cortex	Magnetic pulses to depolarize cerebral neurons	Strong	Non-invasive, approved	Relapse rates, effort, small effect sizes
DBS	Nucleus accumbens, lateral habenula, ventral striatum, inferior thalamic nucleus, peduncle, subgenual cingulate	High-frequency stimulation (130–185 Hz); reduction of neuronal transmission by inactivating voltage-dependent ion channels; modulation of neuronal circuits	Moderate, experimental	Probably highly effective	Implantation procedure
MST	Cerebral cortex	Based on ECT, probably effects increased glucose metabolism	Weak-moderate	Less side effects than ECT	No broad evidence
CES	Probably affects limbic system, reticular activating system, hypothalamus	Electrical currents (<1 mA)	Weak-moderate	Non-invasive, supposed antidepressive mode of action, FDA-approved	No broad evidence
VNS	Left peripheral vagus nerve	(Long-term) modulation of neurotransmitters	Moderate-strong	Anti-suicidal effects and rates of remittance, combination option with nearly all other treatment options, FDA-approved	Latency in antidepressive efficacy

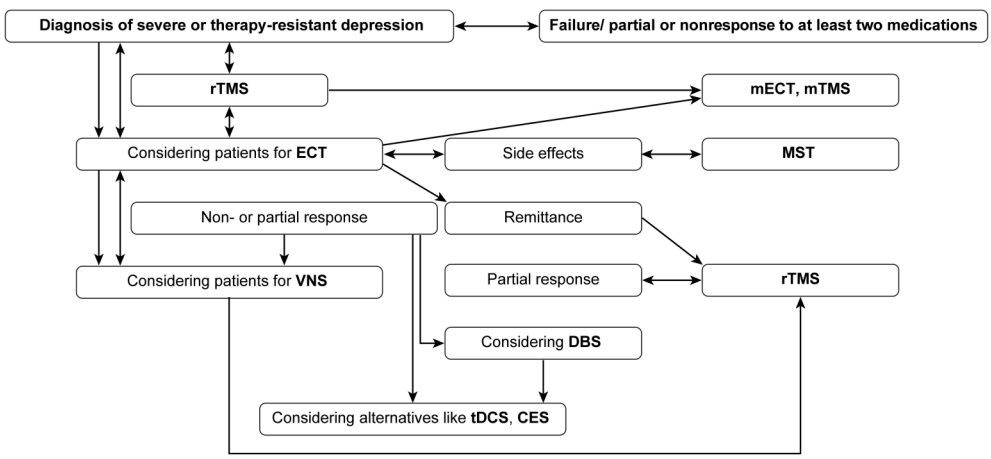

FIGURE 1 | Clinical pathways when choosing neurostimulation techniques.

bradycardia, and, very rarely, asystole; all side effects are generally fully reversible (Elliott et al., 2011; Schneider et al., 2015).

In a nutshell, there is growing and promising evidence for the use of VNS for depression in a 12-month trial. In a recent double-blind trial with 331 TRD patients, adjunct VNS at low (0.25 mA, 130 ls pulse width), medium (0.5–1.0 mA, 250 ls), and high (1.25–1.5 mA, 250 ls) currents was effective over 1 year (Aaronson et al., 2013; Feldman et al., 2013; Muller et al., 2013a).

Smaller studies also showed high levels of remittance of TRD over longer periods (>5 y) (Muller et al., 2013a, 2017a). Recently, Aaronson et al. provided a large set of data showing improved outcomes for adjunctive VNS observed in both ECT responders and non-responders. Within the D-23 VNS registry (489 in the VNS arm and 276 in the treatment-as-usual arm), cumulative remission, based on an MADRS total score, demonstrated that over time, patients in the VNS arm were significantly more likely to experience remission than those in the treatment-as-usual arm (43.3 and 25.7%, respectively), demonstrating significant efficacy. The MADRS is a popular scale because of its high inter-rater reliability and high sensitivity to detect changes in treatment effects. Due to these features, the MADRS has been widely used in mood disorder studies. Higher scores indicate greater symptom severity. As demonstrated in previous studies, the scale has good parallel form reliability. The 5-year cumulative response rate for patients in the VNS arm who had previously responded to ECT was 71.3% compared with 56.9% for the ECT responders in the treatment-as usual arm. For ECT non-responders in the VNS arm, the response rate was 59.6%, compared with 34.1% (95% for ECT non-responders in the treatment-as usual arm). These results show that VNS is promising, particularly, but not only, as a feasible adjunctive tool for ECT responders (Aaronson et al., 2017). In addition to the antidepressive mode of action, a remarkable finding is that VNS seems to have a specific lower all-cause mortality rate and an anti-suicidal effect (Aaronson et al., 2013, 2017; Berry et al., 2013). Therefore, the longer-term results of VNS are encouraging, and VNS can be considered for patients with chronic depression, particularly in situations where treatment resistance may be an issue. A limitation of the available studies on VNS stimulation cited above is the lack of a control group receiving sham stimulation. Sham stimulation is used as a placebo treatment in neurostimulation trials, i.e., specific sham coils, which mimic the feeling of the real stimulation procedure, are used in randomized controlled rTMS trials. Sham stimulation in VNS treatment is much more problematic on an ethical level not only because surgery is required but also because a long period of >6 months of sham stimulation would be required due to the delayed entry of treatment effects under VNS. This seems unethical in light of the seriousness of MDD, including the possible risk of suicide (Aaronson et al., 2013). Thus, the possibility cannot be excluded that a placebo effect influenced the results of the studies cited above. Nonetheless, due to the solid magnitude of effects and the addition of a control group receiving other antidepressive treatment to the large D-23 registry trial (Aaronson et al., 2017), it seems unlikely that the observed effects were due to the placebo effect alone.

CONCLUSION

Selection of Patients for Adjunctive Neurostimulation

The harm of chronic and TRD highlights the need for evidence-based adjunctive treatment options. ECT and others, especially/in addition to rTMS, are primarily delivered for seriously ill depressed probands. Alternative and/or add-on strategies, such as DBS or VNS, should be strongly recommended to patients (**Table 1**, **Figure 1**) as promising adjunctive options to ECT (the gold standard), especially when treatment resistance occurs. Additionally, the combination of rTMS and ECT is promising, and when side effects of ECT occur, MST is a possible alternative. Only ECT and rTMS have level I evidence for regular treatment; VNS is also approved for the indication group for which r-TMS and CES are FDA-approved.

Compared to other neurostimulation techniques, VNS has the advantages of more solid scientific evidence for efficacy compared to MST, tDCS and CES and, after initial implantation, a comparably small burden of time and effort for maintenance treatment compared to ECT and rTMS. Compared to maintenance ECT, VNS is also less invasive in the long term. However, a disadvantage of VNS is the delay of effects after implantation, with substantial treatment effects often only occurring after 3–12 months of treatment.

For MST, tDCS, and CES as adjunctive treatments alone, there is not yet sufficient evidence to recommend them in the first line, but as add-on strategies, they probably should be considered.

In summary, it seems that a special future focus should be placed on therapy based on powerful (especially when combined) augmentative neurostimulation options. Particularly because of the promising results from neurostimulation combination strategies (e.g., ECT followed by VNS and ECT/r-TMS), the expected augmentation effects of combining neurostimulation techniques should be strictly further evaluated in future controlled clinical studies.

AUTHOR CONTRIBUTIONS

HM and AP: Conceived the review's focus; HM, SM, AL, CL, and NB: Conducted the literature review; SM, HM, and NB: Designed the tables and figures; HM and AP: Wrote the first draft, summarized, and finalized the manuscript. All the authors critically commented on drafts, gave expert opinions on neurostimulation and approved the final manuscript.

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Chronic vagus nerve stimulation significantly improves quality of life in treatment-resistant major depression.

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ABSTRACT

Objective
To compare quality-of-life (QOL) change associated with treatment as usual (TAU, any antidepressant treatment) versus adjunctive vagus nerve stimulation treatment (VNS+TAU) in a population of patients with treatment-resistant depression (TRD) for 5 years.

Methods
Self-reported QOL assessments, using the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF), were gathered in a multicenter, longitudinal registry (January 2006– May 2015) comparing the antidepressant efficacy of VNS+TAU versus TAU in TRD. All depressed patients (N=599), with either unipolar or bipolar depression, met DSM-IV-TR major depressive episode criteria and failed at least 4 adequate antidepressant trials. The MontgomeryAsberg Depression Rating Scale (MADRS) was administered by blinded raters. Q-LES-Q-SF scores in the treatment arms were compared via linear regression; linear regression was employed to compare QOL differences with percent decrease in MADRS. A subanalysis comparing Q-LES-Q-SF functional domain change was performed.

Results
328 VNS+TAU and 271 TAU patients with TRD were compared. On average, VNS+TAU demonstrated a significant, comparative QOL advantage over TAU (as demonstrated via nonoverlapping 95% confidence bands) that began at 3 months and was sustained through 5 years and was reinforced using a clinical global improvement measure. Patients receiving VNS+TAU, but not TAU alone, demonstrated a clinically meaningful QOL improvement (34% MADRS decrease) well below the classically defined antidepressant response (50% MADRS decrease). Exploratory post hoc subanalysis demonstrated that VNS+TAU had a significant advantage in multiple Q-LES-Q domains.

Conclusion
Compared to TAU, adjunctive VNS significantly improved QOL in TRD, and this QOL advantage was sustained. Further, TRD patients treated with VNS experienced clinically meaningful QOL improvements even with depression symptom reduction less than the conventional 50% reduction used to ascribe "response."

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Treating Depression with Transcutaneous Auricular Vagus Nerve Stimulation: State of the Art and Future Perspectives

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Depression is a highly prevalent disorder, and its treatment is far from satisfactory. There is an urgent need to develop a new treatment for depression. Although still at its early stage, transcutaneous auricular vagus nerve stimulation (taVNS) has shown promising potential for treating depression. In this article, we first summarize the results of clinical studies on the treatment effect of taVNS on depression. Then, we re-analyze a previous study to identify the specific symptoms taVNS can relieve as indicated by subscores of the 24-item Hamilton Depression Scale in patients with depression. We found that taVNS can significantly reduce multiple symptoms of depression patients, including anxiety, psychomotor retardation, sleep disturbance, and hopelessness. Next, we pose several hypotheses on the mechanism of taVNS treatment of depression, including directly and indirectly modulating the activity and connectivity of key brain regions involved in depression and mood regulation; inhibiting neuro-inflammatory sensitization; modulating hippocampal neurogenesis; and regulating the microbiome–brain–gut axis. Finally, we outline current challenges and lay out the future directions of taVNS treatment of depression, which include (1) intensively comparing stimulation parameters and "dose effect" (treatment frequency and duration) to maximize the treatment effect of taVNS; (2) exploring the effect of taVNS on disorders comorbid with depression (such as chronic pain disorders, cardiovascular disorder, and autism) to provide new "two-for-one" treatment approaches for patients with these disorders; and (3) applying multiple scale methods to explore the underlying mechanism of taVNS.

Keywords: vagus nerve, transcutaneous vagus nerve stimulation, transcutaneous auricular vagus nerve stimulation, depression, brain network, anti-inflammation

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INTRODUCTION

The vagus nerve (VN) is the longest cranial nerve in the human body and is involved in the regulation of multiple systems (1). Due to this wide influence on multiple systems and its important role in maintaining homeostasis, stimulating the VN to modulate the function of related organs has long drawn the attention of investigators (2). As a slow-acting therapy, cervical vagus nerve stimulation (VNS) has been approved by the US Food and Drug Administration for managing treatment-refractory epilepsy in 1997 and for chronic treatment-resistant depression in 2005 (1). However,

surgical risks, technical challenges, and potential side effects have limited the application of VNS (3, 4).

To overcome such barriers of applying invasive VNS (iVNS), non-invasive transcutaneous vagus nerve stimulation (tVNS) methods have been developed. Currently, there are two main ways to apply tVNS. One is to superficially apply stimulation on the cervical nerve using a specially designed device, such as GammaCore, and the other is to apply stimulation on the ear. In this paper, we will focus on the latter. The rationale of tVNS on the ear (transcutaneous auricular VNS, taVNS) is based on anatomical studies demonstrating that certain parts of the ear area (concha and lower half of the back ear over the mastoid process) have afferent VN distribution (5–7). According to the "bottom-up" mechanism of the central nervous system (CNS), electrical stimulation of these areas may produce activity changes in the VN pathway in the brain stem and central structures (8), producing a modulation effect similar to iVNS (9–11). taVNS has been used to treat disorders, such as epilepsy (12, 13), pre-diabetes (14), depression, and chronic tinnitus (15), as well as to boost associative memory (16).

In this manuscript, we summarize the findings of clinical studies on taVNS treatment of depression, re-analyze a previous data set to explore the specific symptoms tVNS can relieve in patients with depression [as indicated by Hamilton Depression Rating Scale (HAMD) subscores] (17), and discuss the potential underlying mechanism, limitations, and future direction of taVNS. Please also see recent review articles on iVNS treatment of depression (2), iVNS/taVNS treatment of chronic pain (18), clinical application (19), and efficacy and tolerability (20).

POTENTIALS OF taVNS TREATMENT OF DEPRESSION AND ITS SIDE EFFECTS

Major depressive disorder (MDD) is a highly prevalent disorder that can significantly reduce quality of life (21). Current treatments for MDD are far from satisfactory (22–24), thereby calling for new treatments for MDD. As a non-invasive peripheral neuromodulation method, taVNS may be a promising treatment option for patients with MDD.

The first taVNS clinical trial on individuals with MDD was performed by Hein and colleagues (9). They investigated the treatment effect of bilateral taVNS on MDD patients using an add-on design (antidepressant therapy with real or sham taVNS). They found that compared to the sham group, the real taVNS group showed significant improvement on the Beck Depression Inventory after a 2-week treatment (five times per week). However, there was no significant difference on the HAMD between the two groups.

In a subsequent non-randomized clinical study with 160 MDD patients (17), we investigated the taVNS treatment effect by training the patients to apply bilateral taVNS at home. The first cohort of patients ($n = 91$) received taVNS for 12 weeks; the second cohort ($n = 69$) first received 4 weeks of sham taVNS followed by 8 weeks of real taVNS. After the fourth week, patients in the taVNS group had greater decreases in the 24-item HAMD score and higher rates of good responders than those of the sham taVNS group. The clinical improvements continued until week 12.

In a recent single-arm study (25), Trevizol and colleagues recruited 12 patients with MDD and tested the effect of taVNS on the bilateral mastoid process (10-session taVNS over 2 weeks). The results showed that 17-item HAMD scores were reduced significantly after the 2-week treatment. All patients exhibited a clinical response, defined as a reduction of HAMD scores of at least 50%. The effect remained 1 month after treatment.

Although the above studies suggest that taVNS can reduce the symptoms of MDD, no study has reported how it can modulate the specific symptoms of MDD patients. To address the question, we re-analyzed the data of our previous study (17) and explored how taVNS can modulate HAMD subscores of patients with MDD (**Table 1**) by performing a repeated measurement analysis with Bonferroni correction to adjust the p-value ($0.05/7 = 0.007$ significance level). We found that compared with sham taVNS, 1-month taVNS can significantly

TABLE 1 | Pre- and post-treatment differences in HAMD subscores between real and sham transcutaneous auricular vagus nerve stimulation (taVNS) cohorts; p values indicating significant difference after Bonferroni correction ($p = 0.05/7 = 0.007$) are marked in bold.

HAMD item	Group	*N*	Pre-treatment (Mean ± SD)	Post-treatment (Mean ± SD)	Post–Pre (Mean ± SD)	Effect size	*p*-Value
Anxiety	taVNS	88	7.2 ± 2.6	5.4 ± 2.4	−1.7 ± 2.4	0.565	**0.001**
	staVNS	60	6.6 ± 1.9	6.0 ± 2.1	−0.6 ± 1.7		
Weight	taVNS	88	0.3 ± 0.6	0.1 ± 0.4	−0.1 ± 0.7	0.025	0.888
	staVNS	60	0.4 ± 0.6	0.3 ± 0.5	−0.1 ± 0.5		
Cognitive disturbance	taVNS	88	4.0 ± 2.7	2.3 ± 1.8	−1.8 ± 2.3	0.458	0.010
	staVNS	60	3.6 ± 1.9	2.7 ± 1.4	−0.9 ± 1.4		
Diurnal variation	taVNS	88	1.2 ± 1.1	0.7 ± 0.9	−0.5 ± 1.2	0.412	0.017
	staVNS	60	0.9 ± 1.0	0.9 ± 1.0	−0.0 ± 1.0		
Psychomotor retardation	taVNS	88	4.9 ± 1.7	3.1 ± 1.7	−1.8 ± 1.8	0.717	**<0.001**
	staVNS	60	4.6 ± 1.3	3.9 ± 1.4	−0.7 ± 1.1		
Sleep disturbance	taVNS	88	4.0 ± 1.9	2.3 ± 1.7	−1.7 ± 1.7	0.575	**0.001**
	staVNS	60	4.1 ± 1.9	3.4 ± 1.9	−0.8 ± 1.5		
Hopelessness	taVNS	88	3.6 ± 1.6	2.0 ± 1.3	−1.5 ± 1.8	0.635	**<0.001**
	staVNS	60	4.1 ± 1.4	3.5 ± 1.6	−0.6 ± 1.2		

reduce multiple symptoms of MDD patients, including anxiety, psychomotor retardation, sleep disturbance, and hopelessness. We also observed a downward trend in cognitive disturbance and diurnal variation (**Table 1**).

Transcutaneous auricular vagus nerve stimulation is a quite safe and well-tolerable treatment method (20). Reported mild/moderate side effects include tinnitus or acceleration of original tinnitus and local problems at stimulation sites, such as pain, paresthesia, or pruritus during or after stimulation (17, 26). Since there are no direct fibers connecting the ear VN to the heart (27, 28), both left and right ears should be safe for applying taVNS. In a recent study (28), Kreuzer et al. measured EKG changes after 24 months of taVNS and found that taVNS has no arrhythmic effects on cardiac function in tinnitus patients with no known pre-existing cardiac pathology. In another study on taVNS treatment of MDD (9), investigators also found that heart rate, blood pressure, and blood test values did not change over the 2-week treatment period.

Interestingly, applying taVNS on the bilateral mastoid process (25) seems to be associated with more severe side effects as compared to taVNS applied on the concha (9, 17). In the Trevizol study (25), of the total 12 patients, 10 patients reported mild to moderate diurnal sleepiness after stimulation, six reported mild to moderate tension headaches with no need for medication, and four reported mild to moderate nausea. We speculate this may be due to the electrical current flowing across the whole brain during bilateral stimulation. Further study is needed to explore the side effects of taVNS on the bilateral mastoid process.

MECHANISMS/HYPOTHESIS ON taVNS TREATMENT OF DEPRESSION

taVNS Can Modulate the Brain Network Associated with the Neuropathology of Depression

A growing body of evidence has shown that depression is associated with structural and functional abnormalities in multiple brain regions involved in emotional processing, self-representation, reward, and external stimulus (stress, distress) interactions (29–37). Based on the limbic-cortical dysregulation hypothesis (38–40), the brain regions involved in MDD are associated with two components: the vegetative-somatic component, including the subgenual cingulate cortex, anterior insula, hippocampus, hypothalamus, and amygdala, and the attention-cognition component, including the dorsal frontal area, dorsal cingulate cortex, inferior parietal cortex, and posterior cingulate cortex. Located between the two components are the basal ganglia and thalamus, which closely communicate with the two components (**Figure 1A**).

Neural anatomy has shown that the auricular branch of the vagus nerve (ABVN) projects to the nucleus tractus solitari (NTS), which is further connected with other brain regions, such as the locus coeruleus, parabrachial nucleus, hypothalamus, thalamus, amygdala, hippocampus, anterior cingulate cortex (ACC), anterior insula, and lateral prefrontal cortex (19, 41). Thus, the VN has direct and indirect connections to the depression-related cortical–limbic-thalamic–striatal neural circuits, influencing the activity of these regions (42–46) (**Figure 1A**).

Recent neuroimaging studies (47–53) found that compared with a control condition, taVNS stimulation can produce activation of the "classical" central vagal projections, e.g., widespread activity in the NTS, dorsal raphe, locus coeruleus, parabrachial area, hypothalamus, amygdala, ACC, anterior insula, and nucleus accumbens. For instance, in a recent study (53), we found that taVNS produced fMRI signal increases in the anterior insula compared to sham stimulation in patients with MDD. The insula activation level during the first stimulation session in the taVNS group was significantly associated with clinical improvement after 4 weeks, as shown by the reduction of HAMD scores. In addition, we found that after 1 month of taVNS treatment, resting-state functional connectivity (rsFC) between the default mode network (DMN), a key network involved in depression (54–60), and the anterior insula and parahippocampus decreased, while the FC between the DMN and the orbital prefrontal cortex and precuneus increased compared with sham taVNS (61). In another study using the same dataset, we found that taVNS can significantly increase rsFC between the right amygdala and left dorsolateral prefrontal cortex compared with sham taVNS (62). These results further endorse the extensive modulation effect of taVNS on brain regions involved in depression.

taVNS May Relieve Symptoms of Depression by Modulating the Inflammation System

Literature suggests that stress initiates cognitive, affective, and possibly biological processes that increase risk for depression (63, 64). Inflammation may play an important role in this process. Specifically, neuro-inflammatory sensitization provoked by stress elicits profound changes in behavior, including common symptoms of depression such as sad mood, anhedonia, fatigue, psychomotor retardation, and social–behavioral withdrawal (63–66). In this process, the hypothalamus, anterior insula, and ACC play an important role (63).

Studies have suggested that the VN plays a crucial role in bidirectionally connecting the brain and immune system, reducing exacerbated inflammation processes outside the CNS (67). Specifically, the VN may participate in the modulation of the inflammation system through two pathways: (1) activating the hypothalamic–pituitary–adrenal axis and suppressing peripheral inflammation *via* glucocorticoids (68) and (2) through the mechanism of the "inflammatory reflex" (67, 69–72) (**Figure 1A**). In the inflammatory reflex, accumulation of inflammatory cytokines activates VN fibers from which afferent signals ascend to the NTS (69). The NTS projects to efferent vagal neurons in the dorsal motor nucleus of the VN, which projects to intrinsic ganglia in the viscera such as in the spleen and liver. Then, acetylcholine is released in the parenchyma of target organs, activating local nAChRa7 macrophages. Production of inflammatory cytokines is inhibited, attenuating the activity of the immune system (73). In addition, VNS may also trigger the vago-sympathetic pathway, i.e., vagal

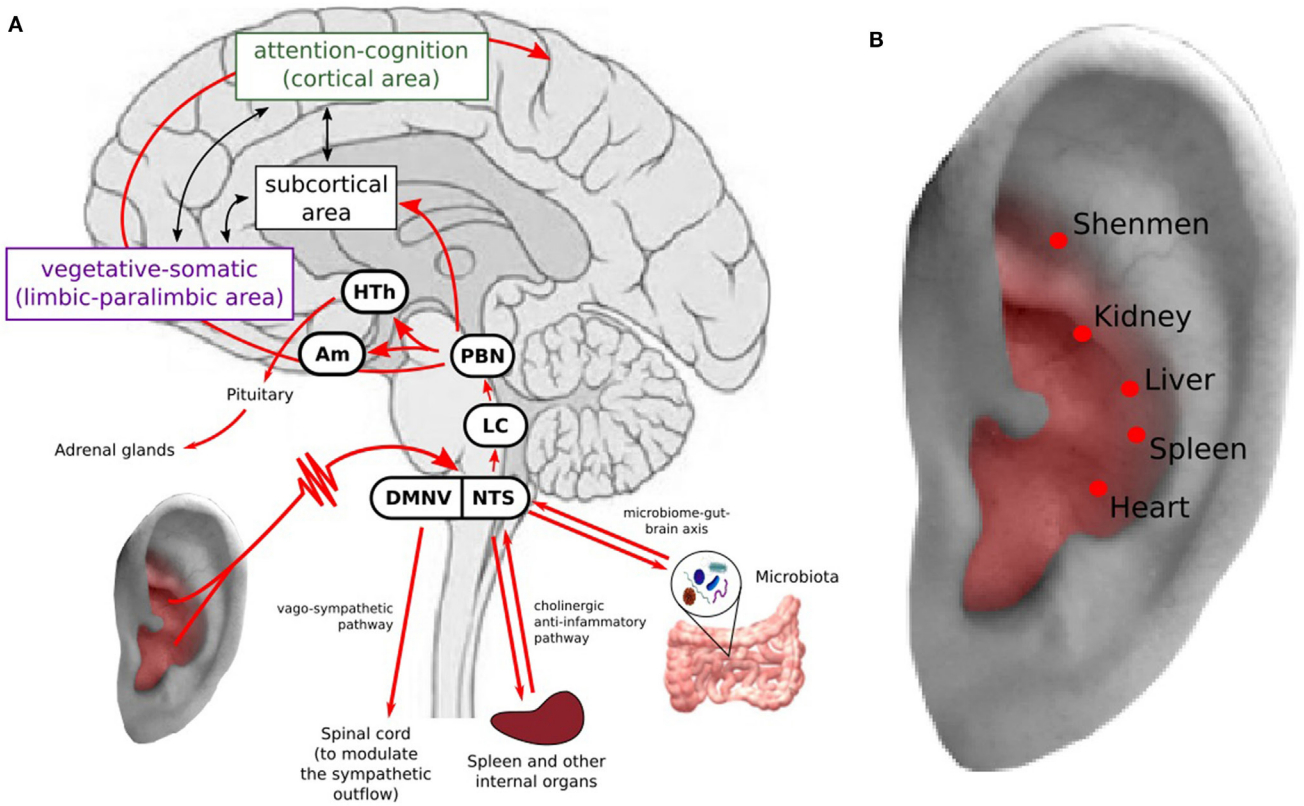

FIGURE 1 | **(A)** Transcutaneous auricular vagus nerve stimulation (taVNS) can modulate the brain network associated with the neuropathology of depression and inhibit inflammation response. Stimulation of the auricular branch of the vagus nerve (VN, indicated in red), which projects to the nucleus tractus solitari (NTS), continuing to the locus coeruleus and parabrachial nucleus. From the parabrachial nucleus, it propagates to various brain regions involved in depression (39, 40). taVNS may inhibit inflammation response to relieve stress and depressive symptoms. HTh, hypothalamus; PBN, parabrachial nucleus; LC, locus coeruleus; NTS, nucleus tractus solitary; DMNV, dorsal motor nucleus of the vagus nerve. **(B)** Auricular acupuncture points used for treating depression and other mental disorders at area with VN distribution.

afferents in the NTS trigger the dorsal motor nucleus of the vagus nerve to modulate the sympathetic outflow by innervating preganglionic sympathetic neurons in the spinal cord (74, 75) (**Figure 1A**).

Other Potential Mechanisms

Recently, accumulating evidence has demonstrated that microbe interactions are crucial in maintaining homeostasis in humans. Studies (76–79) have suggested that gut microbiota can influence brain function, mood, and behavior by interacting with the central nervous system through neural, endocrine, and immune pathways. Particularly, studies have shown that the microbiota is crucial in modulating the stress response and stress-related behaviors, such as depression and anxiety (76, 78–80). It is well-known that the VN can significantly modulate the gastrointestinal, immune, and endocrine systems (1). Thus, taVNS may also regulate the functions of the above systems and achieve a treatment effect in depression by adjusting the microbiome–brain–gut axis (80) (**Figure 1A**).

Also, based on the neurogenic theory of depression (81), depression results from impaired adult hippocampal neurogenesis, and restoration of adult hippocampal neurogenesis leads to recovery. Studies have shown that VNS may stimulate hippocampal neurogenesis, providing another possible mechanism for depression treatment. For instance, studies have shown that VNS can alter the transmission of neurotransmitters, such as serotonin and norepinephrine, which can modulate hippocampal cell proliferation (2). Thus, taVNS may also relieve depression symptoms by modulating hippocampal neurogenesis (2).

taVNS and Auricular Acupuncture—Old Wine in a New Bottle

Stimulating certain areas on the ear to treat disorders is not something new. Acupuncture, an ancient therapeutic method, has a long history of applying stimulation on different parts of the body, including the ear, to treat disorders. Nowadays, auricular acupuncture has become a crucial school of acupuncture and is widely used in acupuncture practice (82). Nevertheless, the underlying mechanism of auricular acupuncture remains unclear.

Transcutaneous auricular vagus nerve stimulation provides a new angle to understand auricular acupuncture (83). For

instance, the auricular acupoints used for depression are also located at the area with VN distribution (**Figure 1B**), Thus, auricular acupuncture and taVNS perform the same or similar treatment procedure guided by different theories. Usichenko et al. found that the analgesic effects of auricular acupuncture may be explained by stimulation of ABVN (83). Further study to verify the specificity of auricular acupuncture will not only deepen our understanding of auricular acupuncture, but also facilitate the development of taVNS and peripheral neuromodulation.

CHALLENGES AND FUTURE DIRECTIONS

Where to Stimulate and How to Stimulate

A neural anatomy study (6) showed that the auricular branch of the VN is mainly distributed on the concha (including the outer auditory canal) and lower half of the back ear. Thus, these areas should be the target of taVNS. Nevertheless, given that the branching of the nerve in the concha is variable across individuals and there are other nerve branches in the area, it remains a challenge to stimulate VN consistently across different individuals.

In a recent study, Kraus et al. (49) compared taVNS-evoked fMRI signal changes at the anterior and posterior sides of the left outer auditory canal. Many brain regions excluding the insular cortex showed fMRI signal changes. The fMRI signals were notably decreased in the parahippocampal gyrus, posterior cingulate cortex, and right thalamus (pulvinar) following anterior auditory canal wall stimulation (49). In another brain imaging study (84), the authors compared the fMRI signal changes evoked by 25 Hz stimulation at the inner tragus, inferoposterior wall of the ear canal, cymba concha, and earlobe (control location without VN distribution). The results showed that stimulation at the inner tragus and cymba concha produced significantly greater activation in the NTS and LC compared with the control location (earlobe). Further ROI analysis showed that only stimulating the cymba concha produced a significantly stronger activation in both the NTS and LC than stimulating the control location.

These results suggest that taVNS at different locations of the ear with VN innervation may modulate different brain pathways, which may be associated with different modulation effects. More studies are needed to systemically investigate the linkage between the brain regions and different ear areas.

Stimulation frequency and intensity are both crucial parameters in taVNS. One may imagine that low-frequency stimulation (2–10 Hz) is not as efficient as higher frequency stimulation (20–30 Hz) which is currently used in iVNS for epilepsy and depression. In reality, investigators have used different frequencies in previous studies with wide ranges [1.5 Hz (9), 20 Hz (17), and 120 Hz (25)].

Studies suggest that different stimulation frequencies could produce different brain changes and neurotransmitter releases (85, 86). In an animal study (87), investigators found that the anti-epileptic effect of 20 Hz taVNS was significantly longer than those of 2 and 100 Hz as measured by the duration of seizure suppression. A recent study (88) on taVNS treatment of drug-resistant epilepsy showed a significant reduction in seizure frequency in patients of the 25 Hz group as compared to the 1 Hz group. However, in another study (26) on migraine patients, investigators found that 1 Hz taVNS produced greater improvement than 25 Hz taVNS. Taken together, these studies imply that the optimal stimulation frequency may vary depending on the disorder.

Likewise, there are few systematic studies on the optimal intensity of taVNS. Previous studies have suggested that stimulation intensity could be set to a level that could arouse a tingling but tolerable sensation (17, 61, 62). In addition, the intensity may interact with frequency [individuals with low frequency stimulation tend to be able to tolerate higher stimulus intensities than those who receive high frequency stimulation (88)]. However, investigators (9) have applied subthreshold taVNS (the patients could not feel the sensation) and relieved symptoms in patients with MDD, which calls for further research on this topic.

Finally, very few studies have been carried out to explore the "dose effect" of taVNS, i.e., how long and how frequently we should apply taVNS. iVNS stimulation usually lasts for many hours per day. Such durations are unrealistic for taVNS. Current studies range from 30-min stimulation durations two times per day (17) to 15-min stimulation durations five times per week (9). Also, if the patients were trained to apply the taVNS by themselves, the problem of compliance is difficult to evaluate and may somehow counterbalance the interest for such a technique.

In summary, investigators have used a wide range of stimulation parameters in taVNS treatment of depression. Identifying the optimal stimulation parameters and "dose" may represent the crucial next step for taVNS research.

Future Directions

(1) Although previous studies have suggested that taVNS holds potential for patients with MDD, the key parameters and "dose" that can maximize the treatment effect remain unknown. Studies to directly compare different stimulation parameters (frequency and intensity), duration, and frequency of treatment are needed. In addition, large randomized clinical trials are also needed to test the treatment effect of taVNS on patients with different age ranges (from children and teenagers to older adults), as well as different depression severities, so that we can have a better idea of the target population for taVNS.

(2) Depression can be comorbid with many other disorders, such as chronic pain (89, 90), cardiovascular disorder (91, 92), inflammatory bowel disease (93), irritable bowel syndrome (94), and autism (95). Thus, it may also provide a new treatment option for "two-for-one" treatment approaches for patients with disorders comorbid with depression.

(3) Multiple scale mechanism studies incorporating brain imaging tools, inflammation markers, vagal tone measurements, and neural transmitters are needed to deepen our understanding of taVNS and facilitate development of new treatment methods for depression and disorders comorbid with depression.

In summary, taVNS can significantly reduce anxiety, retardation, sleep disturbance, and hopelessness symptoms in patients

with depression. Current literature suggests that it may relieve the symptoms of MDD through multiple mechanisms. Further research is needed to identify the optimal stimulation parameters and "dose" of taVNS, testing its effect on MDD patients of different ages and severities, as well as on disorders with comorbid depression.

AUTHOR CONTRIBUTIONS

JK, PR, and JF conceived the idea; JK, PR, JF, JP, and SL did the literature search and prepared figures and manuscript.

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Systematic Review and Meta-Analysis

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Transcutaneous auricular vagus nerve stimulation in treating major depressive disorder

A systematic review and meta-analysis

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Abstract

Background: Transcutaneous auricular vagus nerve stimulation (taVNS), as a noninvasive intervention, has beneficial effects on major depressive disorder based on clinical observations. However, the potential benefits and clinical role of taVNS in the treatment of major depressive disorder are still uncertain and have not been systematically evaluated. Therefore, we performed a systematic review and meta-analysis to evaluate the effectiveness and safety of taVNS in treating major depressive disorder.

Methods: Four electronic databases, namely, Embase, MEDLINE, the Cochrane Library and PsycINFO, were searched for all related trials published through May 1, 2018. We extracted the basic information and data of the included studies and evaluated the methodological quality with the Cochrane risk of bias tool and the nonrandomized studies-of interventions (ROBINS-I) tool. A meta-analysis of the comparative effects was conducted using the Review Manager 5.3 software.

Results: A total of 423 citations from the databases were searched, and 4 studies with 222 individuals were included in the meta-analysis. The taVNS technique could decrease 24-item HAMD scores more than the sham intervention (MD: −4.23, 95% CI: −7.15, −1.31; $P = .005$) and was also more effective in decreasing Self-Rating Depression Scale scores ((MD: −10.34, 95% CI: −13.48, −7.20; $P < .00001$), Beck Depression Inventory scores (MD: −10.3, 95% CI: −18.1, −2.5; $P = .01$) and Self-Rating Anxiety Scale scores (MD: −6.57, 95% CI: −9.30, −3.84; $P < .00001$). However, there was no significant difference in the Hamilton Anxiety Rating Scale scores between the taVNS and sham taVNS groups (MD: −1.12, 95% CI: −2.56, 0.32; $P = .13$). No obvious adverse effects of taVNS treatment were reported in the included studies.

Conclusion: The results of the analysis preliminarily demonstrated that taVNS therapy can effectively ameliorate the symptoms of major depressive disorder, providing an alternative technique for addressing depression. However, more well-designed RCTs with larger sample sizes and follow-ups are needed in future studies to confirm our findings.

Abbreviations: BDI = Beck Depression Inventory, CANMAT = Canadian network for mood and anxiety treatments, DBS = deep brain stimulation, ECT = electroconvulsive therapy, GBD = Global Burden of Disease, HAMA = Hamilton Anxiety Rating Scale, HAMD = Hamilton Depression Rating Scale, iVNS = invasive nerve stimulation, MD = mean difference, MDD = major depressive disorder, ROBINS-I = risk of bias of nonrandomized studies-of interventions, SAS = Self-Rating Anxiety Scale, SDS = Self-Rating Depression Scale, taVNS = transcutaneous auricular vagus nerve stimulation (taVNS), VNS = vagus nerve stimulation.

Keywords: major depressive disorder, meta-analysis, systematic review, transcutaneous auricular vagus nerve stimulation

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1. Introduction

Major depressive disorder (MDD) is a mental disorder that does harm to the physical and psychological health of an individual and, even worse, may lead to suicide. The global prevalence of major depressive disorder was estimated to be approximately 216,047,000 people in 2015 according to the Global Burden of Disease (GBD) study, representing an increase of 17.8% from the measurement in 2005.[1] MDD are characterized by the symptoms of low mood, sadness, isolation and accompanied by several psychophysiological changes that last at least 2 weeks. Although both bipolar depression and unipolar depression are associated with depressive symptoms and functional impairment, bipolar depression accompanies with the feature of mania or hypomania and is observed with more white matter abnormalities in the brain,[2] which needs to be differentiated in order to treat properly. According to the Canadian network for mood and anxiety treatments (CANMAT) clinical guidelines for the management of major depressive disorder, there are many interventions for treating major depressive disorder, including pharmacotherapy, psychotherapy, neurostimulation, and complementary and alternative interventions.[3] However, previous studies found that approximately 30% of patients would resist antidepressants, even though antidepressant medicines are widely used in clinical practice.[4,5] Neurostimulation, such as vagus nerve stimulation (VNS), deep brain stimulation (DBS), or electroconvulsive therapy (ECT), has been recommended and is effective for treatment-resistant depression; however, these interventions also possess a certain risk of developing infections and other potential side effects due to surgical implantation.[6–8] Therefore, it is necessary to find a safe and effective method to address major depressive disorder.

Transcutaneous auricular vagus nerve stimulation (taVNS), as a noninvasive method, has a good efficacy in treating neuropsychiatric disorders.[9] Transcutaneous electrical stimulation of the concha or the lower half of the back ear (afferent vagus nerve distribution), can produce a similar modulatory effect to that of invasive nerve stimulation (iVNS).[10] In recent years, several clinical trials were involved in exploring the therapeutic effects of taVNS for managing major depressive disorder; however, the potential benefits and clinical role of taVNS in the treatment of major depressive disorder are still uncertain and have not been systematically evaluated. Therefore, we performed a systematic review and meta-analysis to assess the efficiency and advantages of taVNS in the treatment of major depressive disorder.

2. Methods

2.1. Search strategy

Four electronic databases, namely, Embase (via OVID), MEDLINE (via OVID), the Cochrane Library/Central Register of Controlled Trials and PsycINFO (via OVID), were searched for all citations published through May 1, 2018. The combinations of medical subject heading terms (MeSH) and free text terms related to major depressive disorder, transcutaneous auricular vagus nerve stimulation and clinical trials were searched for potentially eligible citations. The specific search strategies of each database are listed in appendix 1, http://links.lww.com/MD/C719.

2.2. Selection and exclusion criteria

All clinical trials that met the following criteria were included in the meta-analysis: patients were diagnosed with major depressive disorder; transcutaneous auricular vagus nerve stimulation was used as an intervention; placebo or other non-taVNS were used as a comparison; and randomized controlled trials or nonrandomized controlled trials were used as the study design.

Studies that reported insufficient data or nontarget outcomes were excluded. Conference abstracts, editorials, case reports, and letters were also excluded.

2.3. Data extraction and quality assessment

Data and relevant information were extracted by 2 reviewers (PHL and HLF) independently. Detailed information of the basic characteristics of each study's population, intervention, comparisons and outcomes was extracted. Another 2 reviewers (WTC and CXW) checked for the accuracy of the data and related information and then evaluated the methodological quality of the included studies according to the Cochrane risk of bias tool and the ROBINS-I bias tool.[11,12] Any disagreement was resolved via discussion or was adjudicated by a third reviewer (LML) if necessary.

2.4. Outcomes

The primary outcomes of our study were depression scales, including the 24-item Hamilton Depression Rating Scale (HAMD), the Self-Rating Depression Scale (SDS), and the Beck Depression Inventory (BDI). The secondary outcomes were major depressive disorder-related scales, including the Hamilton Anxiety Rating Scale (HAMA) and the Self-Rating Anxiety Scale (SAS).

2.5. Statistical analysis

The meta-analysis was conducted with Review Manager 5.3 (Cochrane Collaboration, Oxford, UK)). The continuous outcomes were reported as the mean value and standard deviation and were analysed by using the mean difference (MD) with 95% CIs. I-square (I^2), as an index, was used to assess heterogeneity and to determine which statistical model to use to analyse the results. If I^2 exceeded 50% and the P-value was $<.1$, a random-effects model was selected; otherwise, a fixed-effects model was used to analyse the results. Moreover, if the pooled results showed clinical heterogeneity, a subgroup analysis or sensitivity analysis was conducted to solve this issue. Publication bias was estimated by funnel plots or Egger's test. If the number of included studies was <10 or if it was difficult assess publication bias in a study, then Egger's test was performed. Conversely, funnel plots were used to evaluate publication bias.

3. Results

3.1. Study Identification and Selection

The titles and abstracts of a total of 423 citations from 4 databases were screened for initial review. After removing 61 duplicates and 327 studies with unrelated target topics, 35 articles remained for full-text reviews. Three studies (n = 222) met the inclusion criteria and were eligible for further quantitative analyses. Figure 1 shows the specific screening procedure of the PRISMA flowchart.

3.2. Characteristics of the included studies

Among the 3 included studies, there was one randomized controlled trial and 2 nonrandomized controlled trials.[13–15] The

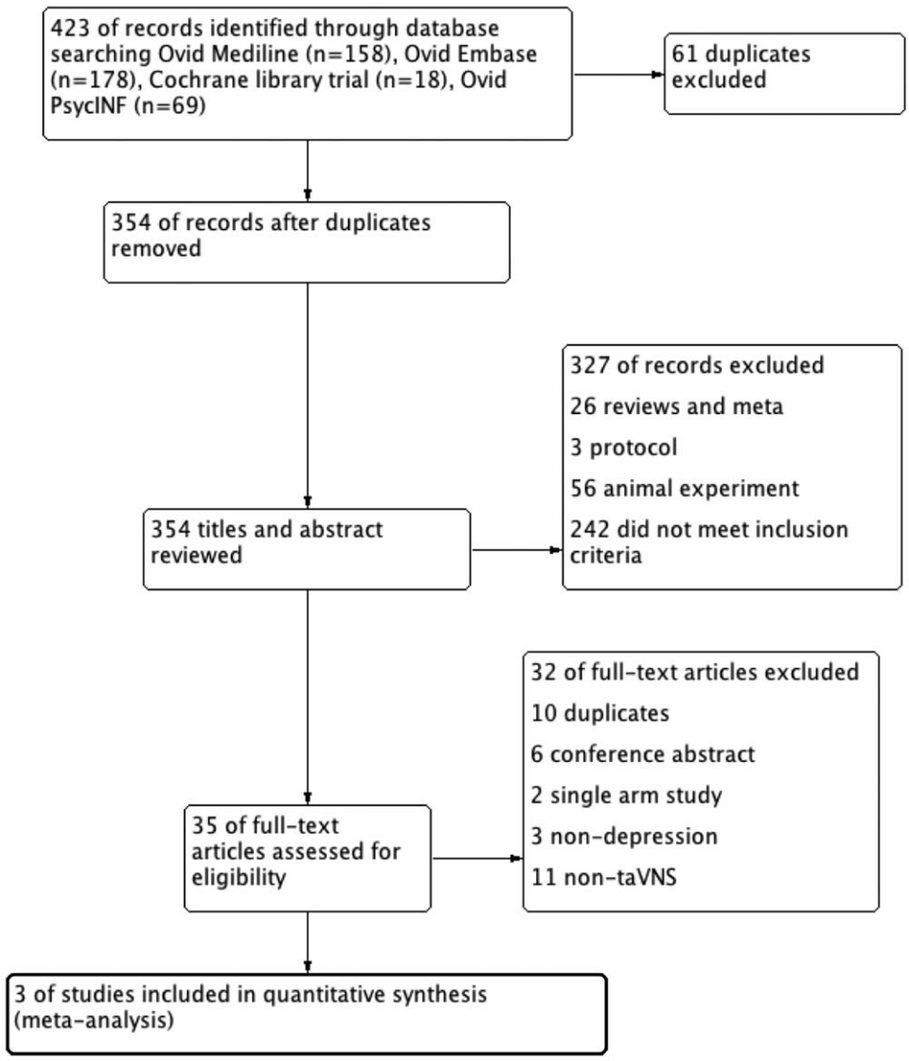

Figure 1. Screening procedure of the PRISMA flowchart.

4 included studies were published between 2013 and 2018. The clinical trials of the included studies were conducted in Germany and China. The sample sizes of the included studies ranged from 37 to 160 patients.

The population of the included studies were all major depressive disorder patients according to the ICD-10 (World Health Organization 1992), and the patients were all in a stable stage. The interventions used in the control groups were all sham taVNS.[13–15] The therapy duration ranged from 2 weeks to 4 weeks. In addition, the frequency of treatment was mostly twice a day or at least 5 days a week. The specific characteristics of the included studies are presented in Table 1.

3.3. Quality assessment of the included studies

We assessed the quality of the included studies according to the Cochrane risk of bias tool and the risk of bias of nonrandomized studies-of interventions (ROBINS-I) tool. One randomized controlled trial[13] reported adequate random sequence generation (selection bias), while concealment of allocation was unclear in this RCT study. In addition, this RCT did not use blinding of either the participants or personnel. The attrition bias and reporting bias of this RCT were low risk. The other 2 clinical trials[14,15] were evaluated with the ROBINS-I tool. All the non-RCT studies did not report confounding biases since the studies were not cohort studies. Two studies[14,15] had a low risk of bias in the selection of participants for the study due to all the eligible subjects for the target trials being included in the study and the interventions being consistent from the start to the end of treatment. Since taVNS was a well-defined intervention in these 2 trials, the bias in classification of the intervention was low. The deviation bias from the intended intervention was low in all 2 studies, as all the studies used a blinding method to mask participants and to reduce the chance of an impact on the outcome. Two trials[14,15] reported drop-out rates that had a low-risk bias of missing data. One study[14] reported that the outcome assessments might not have been influenced by the knowledge of the participants, while the other one trials[15] was unclear as to whether the outcome measures could have been influenced by knowledge of the intervention received by the participants,

Table 1

The characteristics of included studies.

Author	Year	Patients	Intervention1	Intervention2	Outcome	Duration	Frequency	Study design
Hein, E[13]	2013	Major depressive disorder	Transcutaneous auricular vagus nerve stimulation (taVNS) (n=18)	Sham taVNS (n=19)	24- item Hamilton Depression Rating Scale (HAM-D);Beck Depression Inventory (BDI)	2 weeks	15 min once (study 1) or twice a day (study 2)/ 5 days each week	Random clinical trial
Rong,P.J.[14]	2016	Major depressive disorder	Transcutaneous auricular vagus nerve stimulation (taVNS) (n=91)	Sham taVNS (n=69)	24- item Hamilton Depression Rating Scale (HAM-D); 14-item Hamilton Anxiety Rating Scale (HAM-A), the Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS)	4weeks,8, 12weeks	30 min,twice a day;	Non-RCT
Tu,Y.H.[15]	2018	Major depressive disorder	Transcutaneous auricular vagus nerve stimulation (taVNS) (n=20)	Sham taVNS (n=21)	24- item Hamilton Depression Rating Scale (HAM-D); 14-item Hamilton Anxiety Rating Scale (HAM-A), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS)	4weeks	30 min,twice a day; at least 5 days a week	Non-RCT (A single-blinded clinical trial)

resulting in a moderate risk of bias. All the non-RCT studies[14,15] had a moderate risk of selection report bias. The detailed quality assessments of the RCT study and the non-RCT studies are presented in Tables 2 and 3.

3.4. Analysis of outcomes

3.4.1. Primary outcomes

3.4.1.1. 24-item Hamilton Depression Rating Scale (HAMD). Four studies used the 24-item HAMD as their primary outcome. Since the heterogeneity index, namely, I^2, of the pooled results of the 3 studies was 64%, and *P*-value equalled .06, we selected a random-effects model to analyse the pooled results. The 24-item HAMD score decreased more in the taVNS group at the end of treatment than in the sham group (MD: −4.23, 95% CI: −7.15, −1.31; $P=.005$) (Fig. 2).

3.4.1.2. Self-Rating Depression Scale (SDS). Two studies used the Self-Rating Depression Scale (SDS) as a measured outcome. We selected a fixed-effects model since the heterogeneity index I^2 was 0%, and $P=.5$. The pooled results of the SDS score differed between the taVNS group and the sham group at the end of treatment (MD: −10.34, 95% CI: −13.48, −7.20; $P<.00001$) (Fig. 3).

3.4.1.3. Beck Depression Inventory (BDI). One study used the Beck Depression Inventory (BDI) as a measured outcome. The BDI score was significantly decreased in the taVNS group compared to that in the sham group (MD: −10.3, 95% CI: −18.1, −2.5; $P=.01$) (Fig. 4).

3.4.2. Secondary outcomes

3.4.2.1. Hamilton Anxiety Rating Scale (HAMA). Two studies reported the Hamilton Anxiety Rating Scale (HAMA) as a measured outcome. A fixed-effects model was chosen to analyse the pooled results due to the heterogeneity index I^2 being 0%, and $P=.47$. The pooled results showed that the HAMA score was lower (MD: −1.12, 95% CI: −2.56, 0.32; $P=.13$) in the taVNS

Table 2

Risk of bias summary for RCT study: review authors' judgements about each risk of bias item for each included study.

STUDY TYPE: RCT study

Author (Year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hein, E. 2013[13]	Low risk of bias Use a randomized controlled design	Unclear risk of bias No related information	High risk of bias Patients in tVNS and sham tVNS did not use blinding.	Unclear risk of bias No related information	Low risk of bias no patient dropped out at the end of treatment	Low risk of bias The outcome measurements were clearly defined and both internally and externally consistent; and there was no indication of selection of the reported analysis from among multiple analyses; and there was no indication of selection of the trial for analysis and reporting on the basis of the results.	Unclear risk of bias No related information

Table 3

Risk of bias summary for non-RCTs studies: review authors' judgements about each risk of bias item for each included study.

Study Type: non-RCTs studies

Author (Year)	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Rong,P.J. 2016[14]	NI No information	Low risk of bias (i) All participants who would have been eligible for the target trial were included in the study; (ii) For each participant, start of follow up and start of intervention coincided.	Low risk of bias taVNS is a well-defined intervention	Low risk of bias sham taVNS was used to blind the participants and there were no deviations from the intended interventions (in terms of implementation or adherence) that were likely to impact on the outcome.	Low risk of bias Seven participants from the taVNS group dropped from the study; Fifteen participants from the sham taVNS group withdrew from the study.	Low risk of bias The methods of outcome assessment were comparable across intervention groups; and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants	Moderate (i) The outcome measurements are clearly defined and both internally and externally consistent;(ii) There is no indication of selection of the reported analysis from among multiple analyses; (iii) There is no indication of selection of the trial for analysis and reporting on the basis of the results.
Tu,Y.H. 2018[15]	NI No information	Low risk of bias (i) All participants who would have been eligible for the target trial were included in the study; (ii) For each participant, start of follow up and start of intervention coincided.	Low risk of bias taVNS is a well-defined intervention	Low risk of bias sham taVNS was used to blind the participants and there were no deviations from the intended interventions (in terms of implementation or adherence) that were likely to impact on the outcome.	Low risk of bias Reported 3 patients in taVNS group and one patients in sham taVNS group dropped out at the end of treatment	Moderate The methods of outcome assessment were comparable across intervention groups; while the outcome measure was unclear whether it would be influenced by knowledge of the intervention received by study participants or not	Moderate (i) The outcome measurements are clearly defined and both internally and externally consistent; and (ii) There is no indication of selection of the reported analysis from among multiple analyses;(iii) There is no indication of selection of the trial for analysis and reporting on the basis of the results.

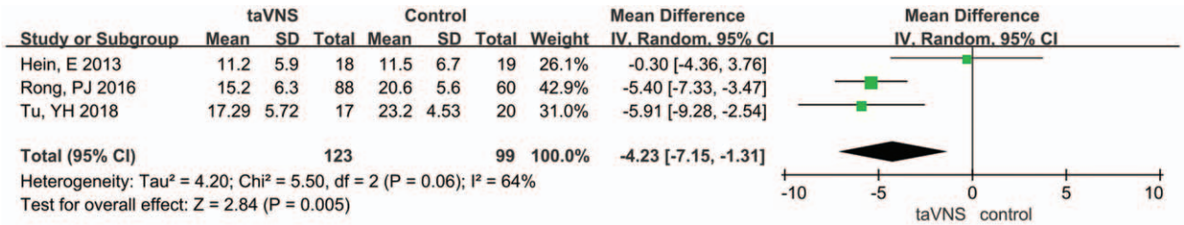

Figure 2. Forest plot of comparison for transcutaneous vagus auricular nerve stimulation (taVNS) versus sham treatment (HAMD outcome). CI = confidence interval, IV = inverse variance, SD = standard deviation.

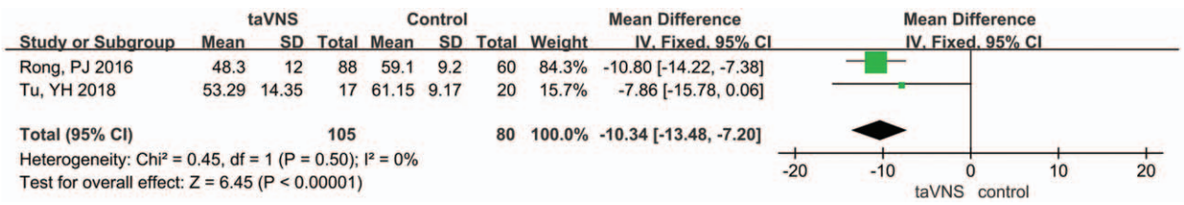

Figure 3. Forest plot of comparison for transcutaneous vagus auricular nerve stimulation (taVNS) versus sham treatment (SDS outcome). CI = confidence interval, IV = inverse variance, SD = standard deviation.

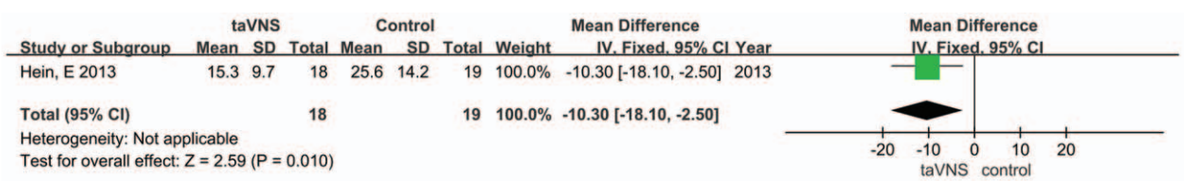

Figure 4. Forest plot of comparison for transcutaneous vagus auricular nerve stimulation (taVNS) versus sham treatment (BDI outcome). CI = confidence interval, IV = inverse variance, SD = standard deviation.

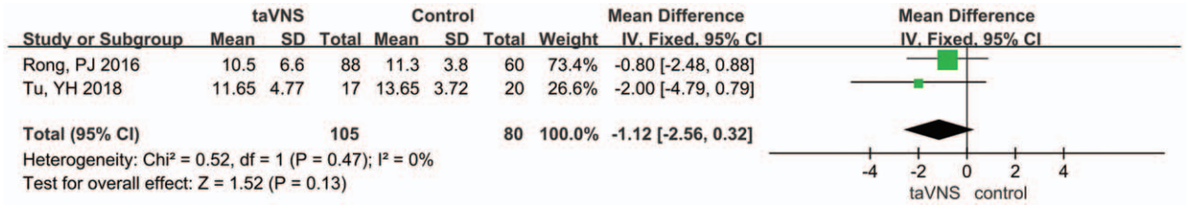

Figure 5. Forest plot of comparison for transcutaneous vagus auricular nerve stimulation (taVNS) versus sham treatment (HAMA outcome). CI = confidence interval, IV = inverse variance, SD = standard deviation.

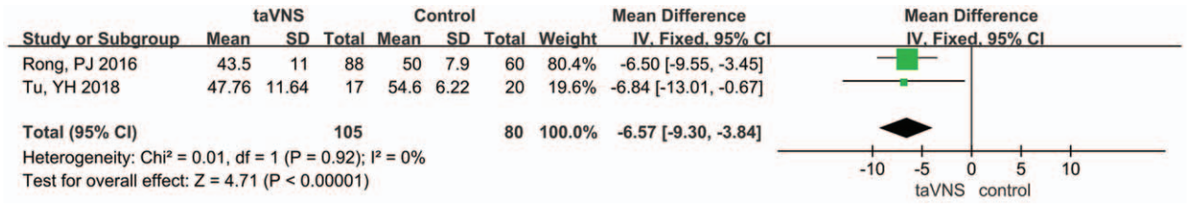

Figure 6. Forest plot of comparison for transcutaneous vagus auricular nerve stimulation (taVNS) versus sham treatment (SAS outcome). CI = confidence interval, IV = inverse variance, SD = standard deviation.

group post-intervention than in the sham group. While there were no significant differences between the taVNS and sham taVNS (Fig. 5)

3.4.2.2. Self-Rating Anxiety Scale (SAS). The Self-Rating Anxiety Scale (SAS) was used as an assessment outcome in 2 studies. The heterogeneity index I^2 was 0%; thus, we selected a fixed-effects model. After combining the results, the pooled results showed that there was a significant difference between the taVNS group and the sham group at the end of treatment (MD: −6.57, 95% CI: −9.30, −3.84; $P < .00001$) (Fig. 6).

3.5. Publication bias

Due to the small number of included studies, a funnel plot did not allow assessment of the publication bias. Therefore, we used Egger's test to evaluate the publication bias. There was no obvious publication bias in included studies when performing Egger's test ($P = .773$). The specific Egger's tests are shown in Table 4.

3.6. Adverse outcomes

One studies recorded the side effects of transcutaneous auricular vagus nerve stimulation in treating major depressive disorder but did not report the adverse outcomes.[15] One study reported that 2 patients who underwent taVNS and 3 patients who underwent sham taVNS had mild tinnitus side effects but recovered quickly after cessation of the taVNS intervention.[14] Another study reported that there were no adverse side effects after the taVNS intervention.[13]

4. Discussion

4.1. Summary of findings

We conducted this meta-analysis by mainly comparing transcutaneous auricular vagus nerve stimulation with sham taVNS. The analysis consisted of 2 study designs, namely, RCTs, and non-RCTs. Normally, RCTs are difficult to combine with other study designs in analysing the results. However, since taVNS is a new and non-invasive intervention for major depressive disorder and considering the ethical and safety concerns, there were few RCT studies involved in studying taVNS. Therefore, it seemed reasonable to combine the results of RCTs and non-RCTs together to explore the potential effects of taVNS on major depressive disorder. After performing a systematic review and meta-analysis, there were several findings as follows.

First, the pooled results of our meta-analysis demonstrated that taVNS could significantly reduce HAMD, SDS, SAS, and BDI scores. The HAMD is the most frequently used and is considered the gold standard for assessing depressive symptoms that includes evaluating the mood, suicide ideation, feelings of guilt, insomnia and other somatic symptoms of depression patients.[16,17] The BDI scale mainly assesses depression patients from a psychodynamic perspective.[18,19] These measured scales can comprehensively and typically evaluate the symptoms of depression. Therefore, the pooled results suggested that taVNS, as a noninvasive therapy, could alleviate the symptoms of major depressive disorder effectively. As the Hamilton Anxiety Rating Scale (HAMA) scores between the taVNS and sham taVNS groups were not significantly different, transcutaneous auricular

Table 4

Egger's test of publication bias of all included trials comparing taVNS with control interventions Egger's test.

Std_Eff	Coef.	Std. Err.	*t*	*P*>|*t*|	[95%Conf.Interval]	
slope	−1.148727	1.049177	−1.09	.471	−14.47979	12.18233
bias	1.588509	4.263738	0.37	.773	−52.58742	55.76444

vagus nerve stimulation might be less effective for ameliorating anxiety symptoms. Previous researchers demonstrated that vagus nerve stimulation was effective for refractory or medication-resistant depression.[20,21] Transcutaneous auricular vagus nerve stimulation intervention also stimulates the auricular vagus nerve (afferent vagus nerve distribution) via transcutaneous auricular electric stimulation without surgical implantation. This intervention is safe and has few side effects compared to vagus nerve stimulation with surgical implantation. One researcher also analysed and summarized the treatment effects and potential mechanism of taVNS on major depressive disorder, indicating that taVNS had beneficial effects of reducing multiple symptoms of depression patients according to the changes of subscores of the 24-item HAMD scale.[22] A portion of major depressive disorder patients may be resistant to antidepressants and may need a variety of therapies to address major depressive disorder.[23,24] Therefore, based on our analysis results, healthcare professionals could recommend that depressive patients select taVNS as an alternative intervention when confronted with resistant or refractory depression.

Second, the adverse events of taVNS intervention were mostly reported to be safe for individuals with major depressive disorder. Only one study[14] reported that 2 patients in the taVNS group and 3 patients in the sham taVNS had tinnitus side effects, which fully recovered after self-adjustment. The side-effect reports of these studies demonstrated that taVNS was a safe therapy for major depressive disorder.

Third, the quality of the included studies showed that only one study used the random clinical trial design,[13] while the other 2 trials used non-RCT designs, and we evaluated the quality using the ROBINS-I tool.[14,15] The 2 non-RCT studies had a low risk of bias in the selection of the participants, classification of interventions, deviations, outcome assessments, and attrition and a moderate risk of reporting selection bias. In contrast, the confounding bias was not reported in any of these 2 trials.[14,15]

4.2. Findings in relation to previous studies and reviews

To our knowledge, our current study was a first systematic review and meta-analysis that evaluated the effectiveness of transcutaneous auricular vagus nerve stimulation in the treatment of major depressive disorder. The previous meta-analyses mainly focused on assessing the effectiveness of vagus nerve stimulation via surgical implantation for managing major depressive disorder.[25–27] Another review conducted a systematic review to assess auricular therapy, including ear buried seeds and transcutaneous vagus nerve stimulation, for treating major depressive disorder.[28] Although this previous systematic review involved taVNS therapy, the review was not comprehensive and included few taVNS studies in the analysis. The above systematic reviews mainly focus on evaluating the effectiveness of vagus nerve stimulation (surgical implantation) or auricular therapy in treating depression, while studies in systematically estimating effectiveness and safety of transcutaneous auricular vagus nerve stimulation in addressing major depressive disorder were still lacking in the current. We only analysed one type of vagus nerve stimulation (transcutaneous auricular vagus nerve stimulation) for treating depression and did not combine with other therapies, thus allowing us to evaluate the clinical effects of taVNS accurately without other confounding factors.

4.3. Limitations

Several limitations in this meta-analysis need to be taken into consideration. First, most of the included studies were non-RCTs, and only one RCT with a small sample size was included in the analysis, which may have weakened the strength of the evidence. Second, all the included studies only blinded patients and did not blind the therapists or the outcome assessors. Although it is difficult to blind the therapists, the outcome assessors could have been blinded to reduce detection bias. Third, only one study reported follow-up surveys, which may influence the evaluation of the long-term effectiveness of transcutaneous auricular vagus nerve stimulation in treating major depressive disorder.

4.4. Implications for clinical practice

We summarized the effectiveness of transcutaneous auricular vagus nerve stimulation for major depressive disorder and determined that taVNS could alleviate the symptom of depression, specifically reducing 24-item Hamilton Depression Rating Scale, Self-Rating Depression Scale, Self-Rating Anxiety Scale and Beck Depression Inventory scores, which may provide clinicians and patients with an alternative intervention for major depressive disorder. However, the evidence was not strong enough since the inclusion of only 3 studies into quantitative synthesis, which encouraged researchers to do more clinical research about taVNS in order to provide robust evidence. In addition, the current conditions and characteristics of taVNS in the treatment of major depressive disorder that we systematically reviewed are convenient for researchers to do in the future clinical research.

5. Conclusion

In conclusion, our systematic review and meta-analysis preliminarily demonstrated that transcutaneous auricular vagus nerve stimulation is an effective and safe method for treating major depressive disorder. The taVNS technique could alleviate the symptoms of depression, providing an alternative technique for patients who suffer a stable depressive disorder and are unwilling to select other invasive therapies. However, more well-designed RCTs with larger sample sizes and follow-ups are needed in future studies to confirm our findings.

Author contributions

TCZ, LLM participated in the study concept and design and manuscript authorization. WCX, LPH, FHL and CWT extracted the data and assessed studies. CSY and LLM analyzed the data. WCX wrote the manuscript and ensured the integrity of the data. All authors read and approved the final manuscript.
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Data curation: Peihui Liu, Huaili Fu, Wentao Chen.
Formal analysis: Shaoyang Cui, Liming Lu.
Writing – original draft: Chunxiao Wu.
Writing – review & editing: Liming Lu, Chunzhi Tang.

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REVIEW Open Access

Neural networks and the anti-inflammatory effect of transcutaneous auricular vagus nerve stimulation in depression

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Abstract

Transcutaneous auricular vagus nerve stimulation (taVNS) is a relatively non-invasive alternative treatment for patients suffering from major depressive disorder (MDD). It has been postulated that acupuncture may achieve its treatment effects on MDD through suppression of vagal nerve inflammatory responses. Our previous research established that taVNS significantly increases amygdala–dorsolateral prefrontal cortex connectivity, which is associated with a reduction in depression severity. However, the relationship between taVNS and the central/peripheral functional state of the immune system, as well as changes in brain neural circuits, have not as yet been elucidated. In the present paper, we outline the anatomic foundation of taVNS and emphasize that it significantly modulates the activity and connectivity of a wide range of neural networks, including the default mode network, executive network, and networks involved in emotional and reward circuits. In addition, we present the inflammatory mechanism of MDD and describe how taVNS inhibits central and peripheral inflammation, which is possibly related to the effectiveness of taVNS in reducing depression severity. Our review suggests a link between the suppression of inflammation and changes in brain regions/circuits post taVNS.

Keywords: Vagus nerve, Transcutaneous auricular vagus nerve stimulation, Depression, Brain network, Anti-inflammation

Background

Major depressive disorder (MDD) is a common, costly, and potentially life-threatening psychiatric illness characterized by anhedonia, reduced energy, rumination, impaired cognition, vegetative symptoms, and suicidal tendency [1]. According to the "kindling theory," subsequent episodes of MDD are correlated with a high number of previous episodes, even with milder stressors [2]. Individuals prone to recurrence may experience residual symptoms, including persistent subclinical depressive symptoms, rumination, impaired attentional control, and cognitive decline from the previous depressive episode [1, 3]. As a result, people with recurrent remitted MDD experience difficulty recovering from negative emotions and exhibit a persistent reduction in positive affect, resulting in a sustained depressed mood [4]. Thus, MDD treatment should aim for full recovery—that is, freedom from symptoms and a full restoration of social function at work [5]. Despite the possibility of its incurring skin irritation or redness, which is its most common side effect, "transcutaneous auricular vagus nerve stimulation" (hereafter, "taVNS") is frequently used in the treatment of MDD, especially for residual symptoms [6].

The most widely used therapeutic alternatives for MDD are antidepressant medications, psychotherapy, cognitive behavioral therapy, deep-brain stimulation, electroconvulsive therapy, and repetitive transcranial magnetic stimulation [7]. However, the response rate of antidepressant medications is unsatisfying, and in up to 35% of patients, MDD remains recurrent and resistant to treatment [8]. In view of such facts, vagus nerve stimulation (VNS) was approved by the United States

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Food and Drug Administration in 2005 as an adjunctive long-term treatment for refractory MDD patients of 18 years of age or older who are not responsive to four or more antidepressant treatment trials [9]. Importantly, VNS has a demonstrated anti-inflammatory effect which might be a significant reason for its efficacy in patients who did not respond to antidepressants [7, 10]. However, this approach is limited by the potential side effects, including surgical complications, dyspnea, pharyngitis, pain and tightening in the larynx, and vocal strain [11, 12]. The auricular branch of the vagus nerve, also known as the Alderman's nerve or Arnold's nerve, innervates the external ear [13, 14], and the efficacy of auricular acupuncture and its antidepressive mechanism may be related to that found for VNS [15]. There is evidence that intermittent and chronic stimulation of the taVNS can greatly improve Hamilton Depression Rating Scale (HAM-D) scores without surgery, compared with the scores obtained in a sham taVNS group, and it is also considered to be highly practical and convenient owing to its strong safety and tolerability profile [16].

The theory behind taVNS postulates that the vagus nerve plays important roles in the relationship between the spleen, gut, brain, and inflammation [17]. It is believed that taVNS is linked to the microbiome–brain–gut axis, which regulates the relationship between brain regions mediating antidepressant effects (e.g., amygdala, ventral striatum, dorsal striatum, and ventromedial prefrontal cortex) and the gut connected with the splenic nerve, which is thought to reduce inflammation [18, 19]. Two meta-analyses have shown that the levels of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-1, and C-reactive protein (CRP), are increased during depressive episodes [20, 21]. The findings of a recent review indicate that activation of immune–inflammatory pathways may affect monoaminergic and glutamatergic neurotransmission and contribute to MDD pathogenesis in at least a subset of patients [22]. Innate immune activation and inflammation have been reported to constitute a pathophysiologic mechanism in a subgroup of depressed patients with elevated inflammatory markers [23]. For example, increased plasma CRP was associated with reduced functional connectivity in a widely distributed network including the ventral striatum, parahippocampus, amygdala, orbitofrontal cortex, insula, and posterior cingulate cortex (PCC) [24], while plasma and cerebrospinal fluid CRP were associated with chemical shift imaging measures of basal ganglia glutamate in 50 medication-free MDD outpatients [25]. In another study, it was postulated that immune dysregulation or chronic inflammation might be present in recurrent remitted MDD [26]. Equally, other authors have found that the mechanism underlying taVNS treatment might be associated with persistent inhibition of neuroinflammatory sensitization [27]. However, taVNS-based biosignatures associated with inflammation-induced neural dysregulation in MDD have not been well characterized to date.

In the present review, we discuss the potential immunologic mechanisms and neuroimaging markers for taVNS treatment of MDD. First, we outline the history of auricular acupuncture. Then, we present the anatomic foundation of taVNS. Next, we focus on the relationship between brain regions or circuits and taVNS. Fourth, we address how taVNS inhibits central and peripheral inflammation, indicating a possible mechanism for its efficacy. Lastly, we describe an important link between taVNS and the microbiome–brain–gut axis.

The history of auricular acupuncture

Contemporary auricular acupuncture is part of traditional Chinese medicine that has recently attracted scientific and public attention as it becomes increasingly accessible to the general public in modern China [28] (see Fig. 1). According to writings dating back to the Chinese *Miraculous Pivot*, part of the *Huangdi Neijing* (*The Yellow Emperor's Inner Canon*), and those of Hippocrates in the West [29], the ear is not isolated but rather is directly or indirectly connected with 12 meridians [30]. Since Dr. Paul Nogier, a French neurologist, created a map of the ear resembling an inverted fetus [31], auricular acupuncture has adopted a more systemic approach, and may serve as a source of alternative nonpharmacologic therapies for MDD. In 1990, the World Health Organization recognized auricular acupuncture as a microacupuncture system that can have a positive impact on regulating whole-body function [32]. By 2002, Peuker and Filler had described a branch of the vagus

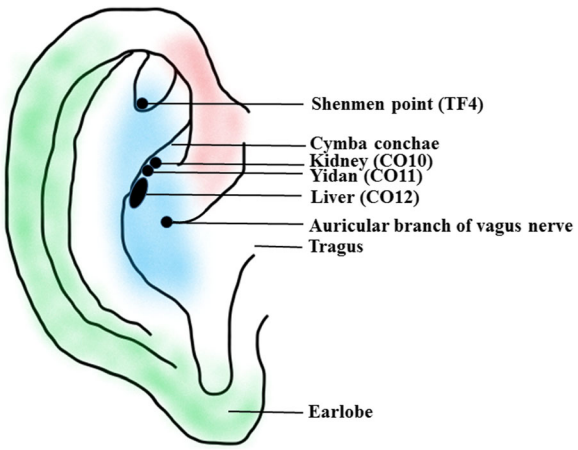

Fig. 1 Innervation of the human auricle, including the auricular branch of the vagus nerve (blue shading); the black areas show the specific auricular acupoints. TF4 and CO10–12 are used to stimulate the auricular branch of the vagus nerve

nerve distributed in the concha (including in the cymba conchae and cavum conchae) [33]. Having considered the anatomy of the neural pathways in the external auricle and their clinical and experimental findings relating to the mechanisms of taVNS, Usichenko et al. [34] proposed that the analgesic effects of auricular acupuncture could be explained by stimulation of the auricular branch of the vagus nerve [34]. Thus, it is very likely that taVNS is derived from the Chinese system of energy circulation along the meridians, which connect "diseased" body organs with the external auricle and explain the reflexotherapy effects of auricular acupuncture [35].

The anatomic foundation of taVNS

The vascularization and innervation of the auricle constitute the theoretical basis of taVNS; thus, similar effects to those obtained with VNS may be achieved by superficially stimulating the area of the ear that has vagus nerve innervation [36]. Using 14 ears from seven German cadavers, Peuker and Filler found that four different nerves are distributed to the external ear, comprising the auriculotemporal nerve, the auricular branch of the vagus nerve, the lesser occipital nerve, and the greater auricular nerve [33]. In the context of the present study, at least, the most important nerve is the auricular branch of the vagus nerve, which supplies most of the area around the auditory meatus and cymba conchae [33]. Burger and Verkuil, however, suggested that the tragus of the auricle is not innervated by the auricular branch of the vagus nerve [37]. Currently, the universally accepted hypothesis relating to taVNS is that external somatosensory inputs interact with internal organ responses and the central neural networks [38].

The vagus nerve consists of 20% motor efferent and 80% sensory afferent fibers, which are important for relaying visceral, somatic, and taste sensations [39]. The brain receives information from the afferent projections of the vagus. The afferent fibers project to the nucleus tractus solitarius (NTS) and locus coeruleus (LC) in the brainstem [40] and then form direct and indirect ascending projections from the NTS to many areas of the brain (e.g., midbrain, hypothalamus, amygdala, hippocampus, and frontal lobe) [41, 42]. A recent systematic review has shown that both the autonomic and the central nervous systems can be modified by auricular vagal stimulation via projections from the auricular branch of the vagus nerve to the NTS [43]. Another review, by Kong et al. [28], showed that the auricular branch of the vagus nerve projects to the NTS, which is further connected with other brain regions, such as the LC, parabrachial area, hypothalamus, amygdala, anterior cingulate cortex, anterior insula, and nucleus accumbens [26]. Functional magnetic resonance imaging (fMRI) and taVNS at the posterior side of the left outer auditory canal have revealed that limbic deactivations are prominent in the area of the parahippocampal gyrus, PCC, and right thalamus [44]. Two fMRI studies carried out during taVNS at the inner side of the tragus or outer auditory canal in healthy subjects have also provided evidence of effectiveness in the generation of blood oxygenation level-dependent signal activations in the LC, nucleus accumbens, thalamus, prefrontal cortex, postcentral gyrus, PCC, and insula [45, 46].

In addition, the vagus nerve regulates the function of the autonomic nervous system from its efferent projections [15]. The vagus nerve runs from the brainstem through the neck to many peripheral organs, including the lungs, liver, stomach, intestines, and spleen [15, 47]. The vagus nerve system suppresses the release of proinflammatory cytokines such as TNF, IL-1β, IL-6, and IL-18 [48, 49]. The spleen is the largest secondary lymphoid organ and hosts a wide range of immunologic functions alongside its roles in the removal of older erythrocytes from the circulation and clearance of blood-borne microorganisms and cellular debris [50]. Given its diverse functions, the spleen allows for interactions between the circulation of immune cells, immune-mediated bacterial clearance, and immune reactivity [51]. Further, the vagus nerve provides extensive innervation to the gastrointestinal tract, where there are substantial depots of lymphoid tissue [52]. Currently, there is some debate concerning the most peripheral branch of the vagus nerve [53], which demonstrates that there are still several unanswered questions regarding the anatomic basis of taVNS [54].

The inflammatory mechanism of MDD

Many biological hypotheses exist with respect to the etiology of MDD, including suppositions incorporating monoamine neurotransmitter disturbance, endocrine system dysfunction, decreased neurotrophic factors, and excessive proinflammatory cytokines in MDD [55]. Among them, inflammatory mechanisms have attracted increased attention, and the inflammatory processes have been found to play an important role in the pathophysiology for at least a subgroup of individuals with MDD [22]. A diverse array of evidence has been reported regarding increased plasma cytokines due to both peripheral chronic inflammation and central microglial activation involved in the pathophysiology of MDD [56]. The relationship between MDD and inflammation is bidirectional, with one predisposing the other [57]. Peripheral stimuli such as chronic infection or stress may inhibit the negative feedback of the hypothalamic–pituitary–adrenal (HPA) axis, trigger the activation of microglia in the brain, and increase the permeability of the blood–brain barrier, resulting in excessive activation of proinflammatory cytokines [26, 58]. On the other hand,

increased proinflammatory cytokines may cause MDD by activating the HPA axis, which results in a depletion of serotonin with an increased activity of the indoleamine-2,3-dioxygenase (IDO) enzyme in the tryptophan–kynurenine system [59]. Studies with animal models as well as clinical research have identified increased plasma inflammatory markers, such as IL-1, IL-2, IL-6, and TNF-α [60]. In some depression cases, chronic inflammation or immune dysregulation has been found to play an essential role in the onset and maintenance of recurrent and refractory MDD [22, 26, 61]. There is a wealth of evidence from randomized control trials suggesting that anti-inflammatory agents are superior to placebos as an add-on therapy and as a monotherapy in MDD patients [62]. These findings on the involvement of low-grade chronic inflammation in the etiopathogenesis of MDD provide further empirical support for the argument that special treatment is needed for subtypes of MDD associated with inflammation.

Relationships between microbiota, MDD, and VNS

The microbiota is a collection of trillions of microorganisms, including 1014 bacteria [63], that is involved in energy harvesting from the breakdown of indigestible food substances, micronutrient absorption, immune system stimulation, neurologically active substance production (e.g., gamma-aminobutyric acid (GABA) and short-chain fatty acids), and HPA axis regulation [64]. Gut microbiota may impact on MDD through a variety of mechanisms, such as the satiety and reward circuits, the HPA axis, immunomodulation, the metabolism of tryptophan, and the production of various neuroactive compounds [64, 65]. Recent work has shown that serum concentrations of immunoglobulin A and immunoglobulin M levels directed against the gut bacteria (i.e., Hafnia alvei, *Pseudomonas aeruginosa*) were significantly higher in MDD patients than in healthy controls [66]. Moreover, probiotic interventional studies offer supportive evidence, in that psychobiotics containing *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* have been found to have the ability to improve depressive symptoms in MDD patients [67]. A clinical study has revealed that gut microbiotic compositions such as Firmicutes, Actinobacteria, and Bacteroidetes were significantly different between MDD patients and healthy controls [68]. In addition, fecal microbiota transplantation from MDD patients into mice has been shown to result in depression-like behaviors [68]. Changes in the overall gut microbiota are relevant to mood states because gut microbiota interact with the brain via the HPA axis or the vagus nerve pathways [69]. Approximately 80% of vagus nerve fibers are afferent and relay signals from the brain to the viscera, including the digestive tract [70]. Microbiota may also indirectly result in MDD through the mediation of the levels of neurotransmitters such as serotonin, noradrenalin, dopamine, and GABA [71].

Neuroimaging biomarkers related to taVNS treatment in healthy participants

To date, six studies have used fMRI to investigate the brain response to taVNS in healthy participants (14, 44–46, 54, 72; see Table 1). Stimulation of the inner tragus and cymba conchae revealed activation of the NTS and the LC, a brainstem nucleus that receives direct input from the tractus solitarius. Stimulation at the inferoposterior wall of the auditory canal revealed the weakest activation of these two nuclei [72]. Using stimulation at the left outer auditory canal, Kraus et al. [46] found increased activation in the insula, precentral gyrus, and thalamus, as well as decreased activation in the amygdala, hippocampus, parahippocampal gyrus, and middle and superior temporal gyrus; stimulation of the posterior wall, however, lead to activation of the tractus solitarius [46]. Using stimulation at the anterior left auditory canal, Kraus et al. [44] found decreased activation in the parahippocampal gyrus, PCC, and right thalamus (pulvinar), and decreased activation in the NTS and LC [44]. Using stimulation of the left inner tragus, Dietrich et al. [45] found increased activation in the left LC, thalamus, left prefrontal cortex, right and left postcentral gyrus, left posterior cingulate gyrus, and left insula, as well as decreased activation in the right nucleus accumbens and right cerebellar hemisphere [45]. Using either left tragus (active) or earlobe (control) stimulation, Badran et al. [54] found increased activation in the contralateral postcentral gyrus, bilateral insula, frontal cortex, right operculum, and left cerebellum in active stimulation and increased activation in the right caudate, bilateral anterior cingulate, cerebellum, left prefrontal cortex, and middle cingulate with the active stimulation versus control stimulation [54]. Furthermore, increased activation was found in the ipsilateral NTS, bilateral spinal trigeminal nucleus, dorsal raphe, LC, contralateral parabrachial area, amygdala, nucleus accumbens, and bilateral paracentral lobule, as well as decreased activation in the bilateral hippocampus and hypothalamus after stimulation at the cymba conchae [14]. In summary, these functional neuroimaging studies of the mechanism of taVNS in healthy participants confirmed the involvement of the NTS and the LC, two structures that are highly associated with the vagus nerve [14, 45], and showed a change in the limbic structures involved in depression-related neural circuits [44, 73, 74].

In addition to the neuroimaging findings in healthy participants, taVNS has also been studied in relation to MDD (see Table 2). Using fMRI and mega-press ^{1}H-magnetic resonance spectroscopy, Li et al. [75] found

Table 1 Prior research—stimulated areas and activated brain regions studied

Study	Stimulated area	Activated brain regions[a]
Yakunina et al. (2017) [72]	The inner tragus and cymba conchae and the inferior posterior wall of the auditory canal	The NTS and the LC
Kraus et al. (2007) [46]	The left outer auditory canal	Increased activation in the insula, precentral gyrus, and thalamus; decreased activation in the amygdala, hippocampus, parahippocampal gyrus, and middle and superior temporal gyrus
	The posterior wall	The NTS
Kraus et al. (2013) [44]	The anterior left auditory canal	The parahippocampal gyrus, PCC, and right thalamus (pulvinar), NTS, and LC
Dietrich et al. (2008) [45]	The left inner tragus	The left LC, thalamus, left prefrontal cortex, right and left postcentral gyrus, left posterior cingulate gyrus, and left insula, as well as decreased activation in the right nucleus accumbens and right cerebellar hemisphere
Badran et al. (2018) [54]	The left tragus (active) or earlobe (control)	The contralateral postcentral gyrus, bilateral insula, frontal cortex, right operculum, left cerebellum and the right caudate, bilateral anterior cingulate, cerebellum, left prefrontal cortex, and middle cingulate
Frangos et al. (2015) [14]	The cymba conchae	Increased activation in the ipsilateral NTS, bilateral spinal trigeminal nucleus, dorsal raphe, LC, contralateral parabrachial area, amygdala, nucleus accumbens, bilateral paracentral lobule; decreased activation in the bilateral hippocampus and hypothalamus

LC locus coeruleus, *NTS* nucleus tractus solitaries, *PCC* posterior cingulate cortex
[a]In healthy participants

increased functional connectivity (FC) between the left rostral anterior cingulate cortex (rACC) and a set of regions including the bilateral precuneus, bilateral insula, right dorsolateral prefrontal cortex (dlPFC), left anterior cingulate cortex, and left middle cingulate cortex, and between the right rACC and left lingual gyrus, but decreased neurotransmitter concentrations of GABA and glutamate in treatment-resistant MDD patients receiving taVNS and sertraline for 8 weeks [75]. Analyzing the hypothalamic subregion FC of 41 mild to moderate MDD patients, Tu et al. [76] found decreased FC between the bilateral medial hypothalamus and rACC in the taVNS group but not in the sham taVNS group. Furthermore, the strength of this FC was significantly correlated with HAM-D improvements after 4 weeks of taVNS [76]. Studying the nucleus accumbens FC of 41 MDD patients receiving continuous real or sham taVNS for 4 weeks, Wang et al. [77] found increased FC between the left nucleus accumbens and bilateral medial prefrontal cortex (mPFC)/rACC, and between the right nucleus accumbens and left insula, occipital gyrus, and right lingual/fusiform gyrus in the taVNS group, compared with the sham taVNS group; the strength of FC between the left nucleus accumbens and bilateral mPFC/

Table 2 Clinical and neuroimaging findings relating to taVNS treatment in MDD

Study	Characteristics of MDD samples	MDD group		Brain regions	Method
		Real taVNS	Sham taVNS		
Li et al. (2019) [75]	Treatment-resistant MDD	1	0	Increased connectivity between rACC and bilateral precuneus, bilateral insula, right dlPFC, left anterior cingulate cortex, left middle cingulate cortex	FC with rACC as seed
Tu et al. (2018) [76]	Mild to moderate MDD	41		Decreased connectivity between bilateral medial hypothalamus and rACC	FC with hypothalamic subregion as seed
Wang et al. (2017) [77]	Mild to moderate MDD	41		Increased FC between left nucleus accumbens and bilateral mPFC/rACC, and between right nucleus accumbens and left insula, occipital gyrus, and right lingual/fusiform gyrus	FC with nucleus accumbens as seed
Fang et al. (2016) [78]	MDD	25		Decreased FC between DMN and anterior insula and parahippocampus, and increased FC between DMN and precuneus and orbital prefrontal cortex	Independent component analysis
Fang et al. (2016) [79]	MDD patients	17	21	fMRI signal increases in the left anterior insula	Task fMRI with taVNS or sham taVNS
Liu et al. (2016) [36]	active and remitted MDD	28	25	Increased FC between right amygdala and left dlPFC	FC with right amygdala as seed

dlPFC dorsolateral prefrontal cortex, *DMN* default mode network, *FC* functional connectivity, *MDD* major depressive disorder, *mPFC* medial prefrontal cortex, *rACC* rostral anterior cingulate cortex, *taVNS* transcutaneous auricular vagus nerve stimulation

rACC was negatively associated with the HAM-D score changes in the taVNS group after 1 month of treatment in the taVNS group, but not in the sham group [77]. Furthermore, decreased FC between the default mode network (DMN) and anterior insula and parahippocampus, and increased FC between the DMN and precuneus and orbital prefrontal cortex have demonstrated in the taVNS group, compared with sham taVNS group; the strength of the increased FC was also associated with improvements in HAM-D scores using the DMN connectivity in MDD [78]. Further, the fMRI signal in the left anterior insula was increased by taVNS, compared with sham taVNS, and the insula activation level was associated with HAM-D improvement in longitudinal 4-week treatment outcomes [79]. Using amygdala resting-state FC changes at baseline and after 4 weeks of taVNS and sham taVNS treatments, our research team reported that there was increased FC between the right amygdala and left dlPFC in the taVNS group, compared with the sham taVNS group; the strength of the increased FC was also associated with HAM-D score reduction, as well as decreases on the anxiety and retardation HAM-D subscales [36]. Taken together, these findings demonstrate that taVNS produces changes in resting-state nodes distributed throughout a wide range of neural networks, including the DMN, salience network (SN) (insula, mPFC/rACC, and parahippocampus), central executive network (CEN) (dlPFC), and reward circuits (orbital prefrontal cortex). A review by Mulders et al. [80] has highlighted an increased FC between the anterior DMN and the SN, an increased FC within the anterior DMN, and a decreased FC between the posterior DMN and the CEN in MDD [80]. Following the work of Mulders et al. [80], in the present study, we propose a model (Fig. 2) focusing on taVNS: decreased FC between the posterior DMN and emotional and reward circuits and increased FC between the anterior and posterior DMN, between the anterior DMN and CEN, and between the CEN and emotional and reward circuits might be more specific to taVNS.

taVNS and the inhibition of central and peripheral inflammation in MDD

Evidence has shown that only specific subpopulations of depressed patients may have an underlying immune dysregulation that could explain depression relapse and lack of therapeutic benefits of antidepressants [22, 81]. Stimuli such as inflammatory, infectious, and stressful challenges might trigger the activation of immune cells in the blood and peripheral tissues, and induce glial cells in the central nervous system to release proinflammatory cytokines [82]. Moreover, peripheral proinflammatory cytokines can reach the brain through leaky regions in the blood–brain barrier, cytokine signaling molecules (including p38 mitogen-activated protein kinase, nuclear factor kappa-light-chain-enhancer of activated B cells, signal transducer and activator of transcription 1a, and cyclooxygenase-2), activation of endothelial cells lining the cerebral vasculature, and binding to cytokine receptors associated with peripheral afferent nerve fibers (e.g., vagus nerve) [83, 84]. Central immune activation (e.g., macrophage accumulation and microglial activation) can affect the levels of acetylcholine through alpha-7 nicotinic acetylcholine receptors (α7 nAChRs) and produce anti-inflammatory effects [85]. During the eradication of invading microorganisms and removal of debris, the activation of α7

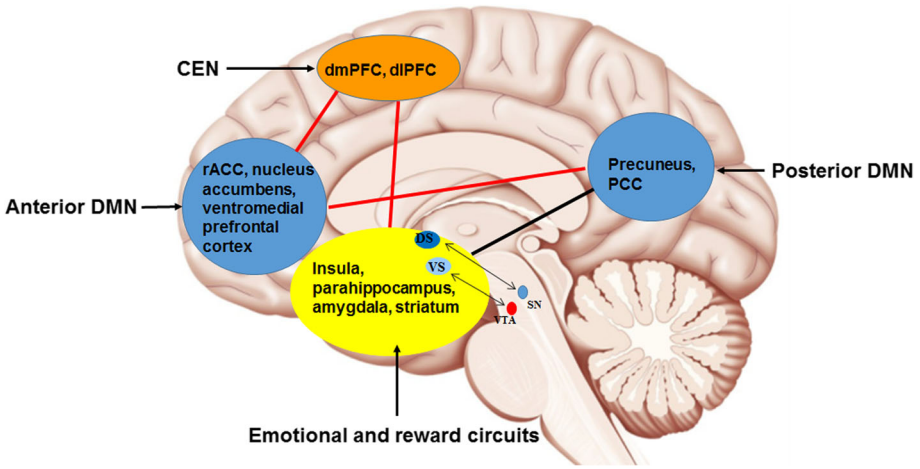

Fig. 2 Proposed model of the mechanism of taVNS in the central nervous system (schematic). Anterior DMN = anterior default mode network; CEN = central executive network; dlPFC = dorsolateral prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; DS = dorsal striatum; LC = locus coeruleus; mPFC = medial prefrontal cortex; NTS = nucleus tractus solitarius; PCC = posterior cingulate cortex; posterior DMN = posterior default mode network; rACC = rostral anterior cingulate cortex; VS = ventral striatum.

nAChRs alters the phenotype from M1-like (activated for antimicrobial activity) to M2-like (resolution, removal of debris) [86] in both peripheral and central macrophages [87]. Wang and colleagues have reported that the α7 nAChR subunit is essential for inhibiting cytokine synthesis by the cholinergic anti-inflammatory pathway (CAP) [88]. Tracey observed that the α7 nAChR induced the cholinergic inflammatory reflex, whereby inflammatory mediators (e.g., cytokines) in peripheral tissues activate the central nervous system via vagal afferents [89]; this, in turn, inhibits proinflammatory cytokine production and protects against systemic inflammation via the CAP that vagus nerve-released acetylcholine inhibits TNF-α release [90] or the connections of the vagus nerve with the spleen [91]. The distal end of the splenic nerve releases norepinephrine, which inhibits the release of TNF-α by spleen macrophages through binding to the β2 adrenergic receptor of spleen lymphocytes that release ACh [92]. Recent review studies have also indicated both peripheral and central anti-inflammatory effects in taVNS, exerted via α7 nAChRs [93].

VNS might have an anti-inflammatory effect on central serotonin levels and affect the HPA axis and cortisol levels [94]. In inflammation, proinflammatory cytokines such as IL-1 and TNF-α increase the activity of IDO [82, 95]. IDO decreases the synthesis of serotonin by catalyzing tryptophan through the production of kynurenic acid, quinolinic acid, and nicotinamide adenine dinucleotide [96, 97]. The depletion of serotonin results in the development of depressive symptoms, as suggested by the monoamine depletion hypothesis [59]. Another mechanism centers on a neuroendocrine pathway involving the HPA axis through a vagus pathway leading to the release of corticotrophin-releasing hormone, adrenocorticotropic hormone, and cortisol by acting directly on hypothalamic and pituitary cells [98, 99]. Thus, taVNS has anti-inflammatory properties both through its afferents (activating the HPA axis) and its efferents (via IDO), putting the vagus nerve at the interface of neurotransmitters, the neuroendocrine system, neuroinflammation, and immunity [100].

Generally, the CAP has an anti-TNF effect exerted by the vagus nerve, which dampens peripheral inflammation and decreases intestinal permeability, thus likely modulating microbiota composition [101]. Moreover, the vagus nerve establishes connections between the brain and the gut and transmits information about the state of the gastrointestinal tract to the brain via afferent fibers [102]. However, the vagus nerve does not directly interact with resident macrophages in the gut; hence, the exact nature of the anatomic interaction between the vagus nerve and the intestinal immune system is still a matter of debate [100]. Recent evidence supports the idea that the central nervous system interacts dynamically with the intestinal immune system via the vagus nerve to modulate inflammation through the HPA axis, IDO, and the CAP [101, 102]. The gut is an important control center of the immune system, in which immune cells are constantly in contact with the external environment, which includes food antigens, nutrients, and potential pathogens [103]. Taking into account the extensive innervation of the gastrointestinal tract, it is not surprising that the vagus nerve appears to play a role in modulating immune activation in the gut wall [104]. The vagus nerve senses microbiota metabolites through its afferents and generates an adaptive response in the regulation of gastrointestinal motility, acid secretion, food intake, and satiety [105]. As a result, taVNS represents a potential treatment for gastrointestinal and psychiatric disorders such as inflammatory bowel disease and MDD [83, 99]. Lim and colleagues found that acupuncture may achieve its treatment effects through vagal nerve–induced anti-inflammatory responses in internal organs [106]. Experimental evidence has suggested that taVNS could decrease the serum proinflammatory cytokines levels, such as TNF-a, IL-1β, and IL-6, as well as the proinflammatory transcription factor; for example, NF-kappa B p65 in endotoxemia was found to affect anesthetized rats [107]. Clinical evidence has suggested that VNS is associated with the abnormal profile of proinflammatory cytokines, such as IL-6, TNF-α, and TGF-β concentrations, in treatment-resistant MDD [108]. Such stimulation might have an anti-inflammatory effect on central serotonin levels and affect the HPA axis and cortisol levels [98]. Activation of the vagus nerve may modulate the neuroimmune system, the neuroendocrine system, and brain regions within the DMN, SN, and CEN (which are the "hotspots" involved in MDD). Therefore, we propose a model focusing on taVNS that can act on three pathways that may treat MDD: (1) regulation of the brain–gut axis through activation of the HPA axis; (2) inhibition of TNF-α release by macrophages through the CAP; (3) direct and indirect modulation of the activity of, and connectivity between, the DMN, SN, and reward circuits. The various mechanisms by which taVNS may improve depressive symptoms are illustrated in Fig. 3.

Conclusions

In summary, we posit that taVNS can significantly reduce the symptoms of depression, such as anxiety, cognitive impairment, sleep disturbance, and feelings of hopelessness. Inflammation interacts with brain circuits via complicated direct and indirect pathways, including neuronal, immune-mediated, and neuroendocrine-mediated signaling. Of note, alterations within and between the DMN, SN, and CEN are "hotspots" involved in MDD, as reported in numerous imaging studies.

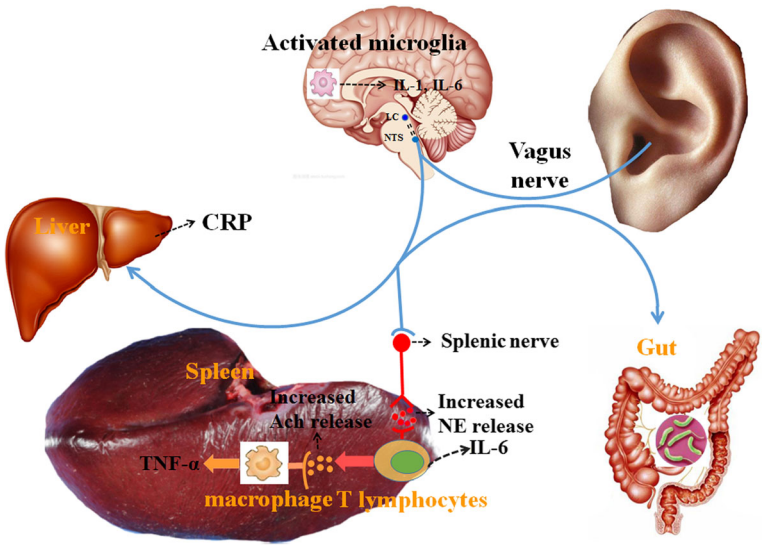

Fig. 3 Hypothesized mechanisms of taVNS in the treatment of depression: direct and indirect modulation of the activity and connectivity of the key brain regions involved in depression, reducing neuroinflammatory sensitization and modulating the autonomic nervous system. ACh = acetylcholine; CRP = C-reactive protein; IL = interleukin; LC = locus coeruleus; NE = norepinephrine; NTS = nucleus tractus solitarius; TNF-α = tumor necrosis factor-α.

taVNS can directly and indirectly decrease connectivity between the posterior DMN and emotional and reward circuits and increase connectivity between the anterior and posterior DMN, between the anterior DMN and CEN, and between the CEN and emotional and reward circuits. We infer that taVNS has anti-inflammatory properties that are exerted through activation of the HPA axis, the CAP, and brain regions or circuits in MDD. Additional studies are needed to further clarify the mechanism of brain function regulation by inflammation in taVNS.

Abbreviations

CAP: Cholinergic anti-inflammatory pathway; CEN: Central executive network; dlPFC: Dorsolateral prefrontal cortex; DMN: Default mode network; FC: Functional connectivity; fMRI: Functional magnetic resonance imaging; HAM-D: Hamilton depression rating scale; HPA: Hypothalamic–pituitary–adrenal; IDO: Indoleamine-2,3-dioxygenase; IL: Interleukin; LC: Locus coeruleus; MDD: Major depressive disorder; mPFC: Medial prefrontal cortex; NTS: Nucleus tractus solitarius; PCC: Posterior cingulate cortex; rACC: Rostral anterior cingulate cortex; SN: Salience network; taVNS: Transcutaneous auricular vagus nerve stimulation; TNF-α: Tumor necrosis factor-alpha; VNS: Vagus nerve stimulation; α7 nAChR: Alpha-7 nicotinic acetylcholine receptor

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Authors' contributions

This work was primarily written by Chun-Hong Liu, Ming-Hao Yang, Guang-Zhong Zhang, Xiao-Xu Wang, Bin Li, Meng Li, Marie Woelfer, Walter Martin, and Lihong Wang. Figures were produced by Chun-Hong Liu and Xiao-Xu Wang. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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REVIEW
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A Review of Parameter Settings for Invasive and Non-invasive Vagus Nerve Stimulation (VNS) Applied in Neurological and Psychiatric Disorders

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Vagus nerve stimulation (VNS) is an established form of neuromodulation with a long history of promising applications. Earliest reports of VNS in the literature date to the late 1800's in experiments conducted by Dr. James Corning. Over the past century, both invasive and non-invasive VNS have demonstrated promise in treating a variety of disorders, including epilepsy, depression, and post-stroke motor rehabilitation. As VNS continues to rapidly grow in popularity and application, the field generally lacks a consensus on optimum stimulation parameters. Stimulation parameters have a significant impact on the efficacy of neuromodulation, and here we will describe the longitudinal evolution of VNS parameters in the following categorical progression: (1) animal models, (2) epilepsy, (3) treatment resistant depression, (4) neuroplasticity and rehabilitation, and (5) transcutaneous auricular VNS (taVNS). We additionally offer a historical perspective of the various applications and summarize the range and most commonly used parameters in over 130 implanted and non-invasive VNS studies over five applications.

Keywords: VNS, taVNS, tVNS, parameter optimization, neuroplasticity, rehabilitation, epilepsy, depression

INTRODUCTION

The earliest description of electrical stimulation of the vagus nerve began in the 1880's in New York. Dr. James Corning applied an electric current as an adjunct to his carotid compression fork; other adjuncts included a neck belt and a lower body vacuum chamber. His cases were anecdotal with limited records of the parameters used. Corning argued his device could prevent or terminate seizures by physically compressing blood flow and modifying parasympathetic tone (Lanska, 2002). Since then, researchers have been seeking to refine and optimize vagus nerve stimulation VNS parameters to treat a variety of neuropsychiatric and medical disorders. Stimulation parameters have a significant bearing on the efficacy of neuromodulation, and here we will describe the longitudinal evolution of VNS parameters in the following categorical progression: (1) animal models, (2) epilepsy, (3) treatment resistant depression, (4) neuroplasticity and rehabilitation, and (5) auricular VNS. Each section summarizes the range and most commonly used parameters,

while the body of text describes individual studies in a historical narrative. Tables are included summarizing the parameters at the completion of each section.

When discussing parameters of VNS, we most commonly refer to parametric factors that affect the administration and delivery of any electrical stimuli. These influence effective dosage. We establish the important terms throughout the review here:

(a) *Pulse width* is the length of time of a square pulse of current. This time parameter is in microsecond (μs) unit.
(b) *Current intensity* is a measure of the amplitude, or strength, of the electrical pulse. This is in milliampere (mA) unit. Current intensity is a specific parameter in constant current (current-controlled) neurostimulation applications, where an electrical pulse generator varies voltage based on resistance of tissue to maintain stable current intensity. VNS is most often delivered as current-controlled. Current-controlled stimulation has several advantages over voltage-controlled stimulation, including safety and precision control of stimulation. Although VNS may theoretically be administered using voltage-controlled stimulators, current-controlled is the standard for this application.
(c) *Frequency* is a measure of total period cycles (the start of a pulse to the start of the next pulse) in a second. Unlike pulse width, it considers the time with no applied current. This is in hertz (Hz).
(d) *On-Off Time* is the amount of time stimulation and non-stimulation epochs are delivered for during a specific period. The "ON" period is the time that stimulation is delivered above an intensity of 0 mA. The "OFF" period is where no stimulation is delivered (0 mA). In practice, this establishes periods of active stimulation interspersed with periods of rest. If ON/OFF periodic rhythms are delivered as part of intervention, these periods are often repeated for the duration of the intervention.
(e) *Duration* of stimulation is the cumulative time of VNS treatment. For example, a patient receiving daily VNS for 6 months has a duration of 6 months. It is an imprecise measure of dosage because it does not convey how much stimulation is in that time. The significance of duration is that it considers the effect of cumulative dosage.

While many of these parameters have very standard definitions, some of them do not; terms like "duration" are inconsistent across papers to refer to different scales of time. The terms listed above serve simply as an operational platform for discussion here.

Lastly, **Figures 1A,B** present visual representations of these parameters as simplified electrical waveforms.

EARLY ANIMAL MODELS AND MECHANISM

Early Animal Work

Bailey and Bremer (1938) used cats to study the afferent effects of the vagus nerve. This study administered electrical current through nerves proximal to where they severed them and recorded electrograms from the cortex, finding some general activity in the frontal lobe. Regarding parameters, there are still many gaps in this early period; frequency was recorded between 24–50 Hz, and current was "of sufficient strength to evoke a maximal cardiomoderator reflex" (Bailey and Bremer, 1938). Though they tried to control this by creating an "isolated encephalon" model, they did note that blood pressure changes could still affect their measurements. The significance of this in the early work is that it was yet unclear whether VNS had a direct effect on the brain or if it was an effect secondary to peripheral activation.

The next major group known to study VNS in animals was Zanchetti et al. (1952), who used a similar isolated encephalon cat model to Bailey and Bremer. Their findings reveal that VNS could decrease spontaneous cortical spindles and convulsion spindles induced by strychnine. This study used 500 μs pulses from 2–300 Hz; intensity was reported only through the voltage (0.1–2 V) (Zanchetti et al., 1952).

Current scientific standards require more parameters than these measured or reported, so it is hard to draw direct comparisons to later work. However, the work of the aforementioned scientists showed that VNS may act in the CNS (Bailey and Bremer, 1938; Zanchetti et al., 1952; Lanska, 2002).

Further experiments in the 1960s used VNS and EEG to differentiate afferent nerve conduction speeds and subsequent effects (Chase et al., 1967; Chase and Nakamura, 1968). However, this period of VNS research was so parametrically diverse that it is difficult to compare many of these papers. There are wide ranges of parameters even within individual papers, while other parameters are entirely missing until later decades (e.g., current intensity, time administered, and ON-OFF time).

Towards the end of the century, when interest in VNS for epilepsy gained momentum, the core parameters largely stabilized – even in the animal models. For example, Zanchetti et al. (1952) tested across a frequency range of 2–300 Hz; by comparison, almost every animal paper from 1995-onward used either 20 or 30 Hz (Naritoku et al., 1995; Krahl et al., 1998, 2001; Manta et al., 2009; Raedt et al., 2011; Furmaga et al., 2012; Pena et al., 2013; Hays et al., 2014a). Pulse width in animals varied considerably; several papers used 500 μs in the 1990s and early 2000s (Naritoku et al., 1995; Krahl et al., 1998, 2001; Manta et al., 2009). Later pulse width was commonly at 100 μs from around 2010 onward (Hays et al., 2014a,b; Borland et al., 2016; Buell et al., 2019). Current intensity was less consistent, but most papers tended to use less than 1 mA, with 0.8 mA being somewhat more common than others (Hays et al., 2014a; Borland et al., 2019; Buell et al., 2019; Meyers et al., 2019). This was true across studies, many of them for epilepsy but also for other sub-fields including spinal injury, depression, auditory plasticity, and memory; many others simply looked for mechanisms of VNS effects.

Central Effects of VNS

It is important to consider the afferent, central effects of VNS when discussing potential behavioral effects. Some of the research has looked at the vagus nerve itself, which suggested that small unmyelinated slow-conduction fibers carry the effective

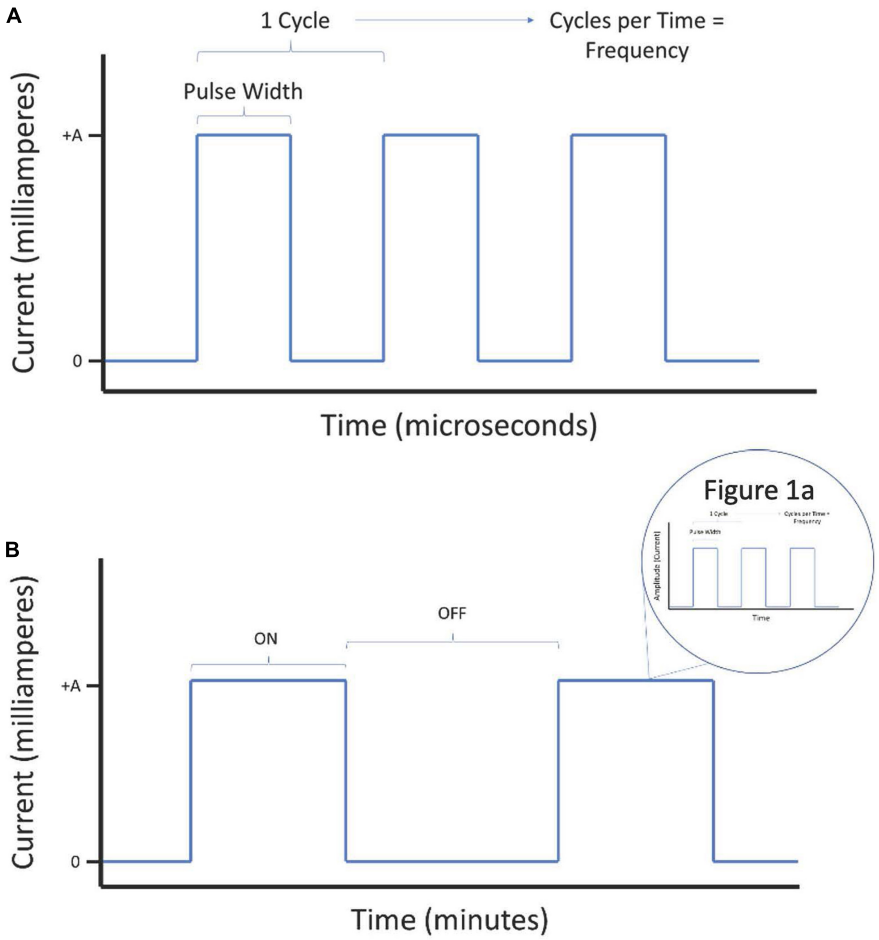

FIGURE 1 | Visual representation of electrical waveform parameters for consideration during administration of vagus nerve stimulation (VNS). The parameters described in the introduction are outlined here on a short time scale **(A)** as well as on a long time scale **(B)**.

signal (Woodbury and Woodbury, 1990; Zabara, 1992). This was challenged by an experiment which selectively lesioned these fibers in rats but did not take away from the anti-epileptic effect (parameters 500 μs, 20 Hz, and 1 mA) (Krahl et al., 2001). Further research would start to shed light on the next steps in this pathway. While there is not a complete model, there is some foundation. Several areas of the nervous system have been proposed, such as the Nucleus Tractus Solitarius and Reticular Formation, as well as more general GABAergic systems, that might be behind the anti-epileptic effects (Woodbury and Woodbury, 1990). C-fos immunostaining in rats showed a broader idea of afferent areas; the parameters used (500 μs pulses, 30 Hz, 30 s ON/5 min OFF, 3 h duration, and 1 mA) resembled those used in human treatments. Using those parameters, the researchers found activations in vagus nuclei, the solitary nucleus, the locus coeruleus, cochlear nucleus, posterior amygdaloid nucleus, cingulate cortex, retrosplenial cortex, hypothalamic nuclei, and the habenular nucleus of the thalamus. They speculated that the limbic system and related areas might account for treating limbic seizures. They also speculated that the noradrenergic locus coeruleus and the solitary nucleus that connects to it might have anti-seizure activity as well (Naritoku et al., 1995).

Research further tested the structure models using similar settings (500 μs, 20 Hz, 30 s ON, and 0.8 mA) with lesions to the LC. In these rats, VNS did not have an antiepileptic effect. This strongly supports the essential role of the noradrenergic LC (Krahl et al., 1998). Using similar parameters, other lesion studies replicated the LC effect and found similar effects with the serotonergic dorsal raphe (500 μs, 20 Hz, 30 s/5 min, and 0.25 mA) (Manta et al., 2009). Blocking alpha-2 signaling with higher frequency (30 Hz) and current (1 mA) and shorter pulse width (250 μs) decreased VNS effects on hippocampal noradrenaline (Raedt et al., 2011). LC lesions also negated antidepressant effects of VNS (250 μs, 30 Hz, and 0.2–0.7 mA) (Grimonprez et al., 2015). Both studies used ON/OFF times of 7 s/18 s, which is a shorter ON time but higher duty cycle than the commonly used 30 s/5 min. Another study depleted norepinephrine and serotonin with immunotoxins and found that they were also necessary for VNS in motor plasticity; the parameters used (100 μs, 30 Hz, 500 m s ON train, 1 week of treatment, and 0.8 mA current) have important differences

compared to many epilepsy experiments, so it is promising to see similar neurotransmitters across applications (Hulsey et al., 2019). Acetylcholine depletion further could decrease VNS-paired motor plasticity using parameters similar to Hulsey et al. (2019); Meyers et al. (2019).

Parametric optimization can take advantage of the established neurocircuitry involved to begin to uncover best parameter combinations. Norepinephrine release has been reliably demonstrated to be increased by VNS (12, 23). Hulsey et al. (2017) demonstrated that this is not as straightforward as believed, as higher pulse width and amplitude increase LC firing rate, however, modulating frequency only impacts timing (not firing rate). Current intensity is also shown to be an important parameter as increasing the intensity increases norepinephrine in the cortex and hippocampus (Roosevelt et al., 2006). It is important, however, to understand that more is not always better, as Borland et al. (2016) demonstrated lower neuroplastic effects at the cortex as a function of increased current intensity suggesting a non-monotonic relationship. Activity within the LC and concentrations of neurotransmitters serve as a strong foundation in optimization of VNS parameters.

Animal models have laid the foundation of VNS in almost every application. There are several other studies examined in this section and in **Table 1** that are not discussed in detail (Farrand et al., 2017, 2019; Stakenborg et al., 2017; Huffman et al., 2019).

VNS FOR EPILEPSY

Epilepsy Animal Models

The Corning Fork of a prior century, initially thought to reduce seizure frequency and long out of use, had a modern successor. Many of the early animal papers focused on EEG and generally revolved around the question: does peripheral vagus stimulation activate the CNS and impact seizures? In the mid-1980s, Zabara (1985 and 1992) used strychnine or PTZ in dogs as a model of seizure. He found that VNS could not only terminate a seizure but could prevent seizures even for some time after VNS stopped. As seen in previous research, cutting the vagus distally did not prevent the effect. Zabara tested a range of pulse widths, frequencies, and current intensities, and suggested that the optimal parameters were ∼200 μs, 20–30 Hz, and 4–20 mA, respectively (Zabara, 1985, 1992). Lockard et al. (1990) similarly, studied VNS moderating provoked seizures in monkeys. Their results were similar, and they studied wide ranges of parameters in their pilot and replication studies. Pulse width was 500–600 μs; currents were 3, 5, or 7 mA; there were many frequencies between 80 and 250 Hz. Where Zabara (1992) used a 30 s ON time, Lockard et al. (1990) stimulated for the duration of a seizure episode or for 40 s after an hour of no seizure activity (Lockard et al., 1990).

There are a few points to make about the canine and primate studies in the context of the larger body of animal VNS work, mostly conducted in rodents. Canine and primate studies used current intensities higher than 1 mA, which is higher than what most research would use for both rat and human VNS for epilepsy. On the other hand, Zabara's optimized frequency in dogs was similar to what would be used in rats and humans; 20–30 Hz is also regularly used in VNS outside of epilepsy (Zabara, 1985, 1992; Lockard et al., 1990). For comparison, a rat study at that time had similar anti-seizure results but concluded with different optimal parameters: 500–1000 μs, 10–20 Hz, 60 s ON time, and 0.2–0.5 mA per mm^2 of nerve cross-section (Woodbury and Woodbury, 1990). Another group used rat models at 500 μs and 20 Hz (Krahl et al., 1998, 2001). We can compare VNS studies between species, but it is important to consider that it seems different research groups have settled on different optimal levels even within species.

Human Epilepsy Trials

Early research on VNS by Zabara had strongly suggested that it would be an effective treatment for seizures, but work remained to show the anti-epileptic effects in humans. Early published data comes from a preliminary paper by Penry and Dean (1990). They tested a range of parameters adapted from the animal models: 130 or 250 μs pulses, 40/47/50 Hz, 29 or 57 s ON, 5 or 10 min OFF, 20 weeks duration (with no stim weeks 8–12), and 1–3 mA as tolerated by their four patients. They saw some reduction in seizure frequencies in three of the patients (Penry and Dean, 1990).

Uthman et al. (1993) used slightly different VNS parameters (500 μs pulses, 50 Hz, up to 120 s ON, 5–20 min OFF, 20 weeks duration with no stimulation weeks 8–12, and current increased as tolerated from 1 mA) in fourteen patients and decreased average seizure frequency by over 45%. They used similar treatment duration and intensity but longer pulse widths and ON periods within each stimulus (Uthman et al., 1993).

Soon after, Wilder et al. (1991) set up a similar study using more patients over at least 24 weeks duration. In this trial, there was a range of initial parameters (250–500 μs, 30–50 Hz, 30–60 s ON, 10–60 min OFF, and current 1 mA), and they adjusted each patient's parameters throughout the study. They reported the end parameters had 30 s ON, 20–50 Hz, and 1–2 mA of current; in discussion they wrote that the best results were 250–500 μs pulses, 20 Hz, around 5–10 min of OFF time, and high but tolerable current at 2 mA. Using these parameters, they concluded that the technology was safe, tolerable, and possibly efficacious (Wilder et al., 1991).

It is important to note that those papers so far mentioned have an important caveat. In each paper, patients had "control periods" of no stimulation. As Wilder et al. (1991) noted, there was an apparent cumulative long-term effect of treatment, so how valid could those control periods truly be? Though these were not parametric studies, the numbers used here are largely the methodological foundation of future work.

Ben-Menachem (1994 and 1999) followed up on this research with a randomized, controlled, double-blind study for partial seizures. Instead of comparing patients to their own control periods, they compared high and low stimulation. "High" stimulation, meaning parameters previously thought to be effective, was compared to "low," or ineffective. What they published as "typical" high stimulation were 500 μs, 30 Hz, 30 s ON 5 min OFF, 1.5 mA current, and over a total duration of 14 weeks. By comparison, they set typical low stimulation

TABLE 1 | Animal Models (Summary parameters of 36 studies).

	Pulse Width	Frequency	On/Off time	Time administered	Current
Most common Parameter	100 μs (18 uses)	30 Hz (20 uses)	500 m s ON (15 uses)	5 w (3 uses)	0.8 mA (18 uses)
Range of Parameters	100 μs – 4 m s	2–300 Hz	125 m sec – 30 min ON/ 17.5 s – 5 min OFF	30 s – 6 w	0.2–10 mA

at 130 μs, 1 Hz, 30 s/90 min, and 1.25 mA. In summary, the control group had shorter pulses, less current, lower frequency, and longer OFF periods. Their results showed that "high" VNS was tolerable and effective (Ben-Menachem et al., 1994a, 1999). George et al. (1995) and Handforth et al. (1998) used similar parameters against a "low" active control to study partial seizures (George et al., 1995; Handforth et al., 1998). A meta-analysis confirmed that the canonical "high" stimulation had an effect on >50 and >75% decreases in seizure frequency (Ghani et al., 2015).

DeGiorgio et al. (2001) completed a retrospective study of a long-term VNS trial. They analyzed each of the main parameters (pulse width, current, frequency, and ON/OFF time) in patients over 12 months. Though the trial had active and control, the clinicians could adjust the parameters every few months within the range approved for FDA treatment. The analysis found that there may have been some correlation between lower OFF times and response rate and seizure frequency; they argued that the data shows a beneficial effect of lowering OFF-time for those who are initially resistant to treatment. However, more importantly, they did not find any statistically significant association between any other parameter and treatment effect (DeGiorgio et al., 2001).

In a later paper they noted that many of the parameters had a history of uncontrolled studies and possible confounds. They designed a study to focus specifically on ON/OFF times as a duty cycle: 7 s/18 s, 30 s/30 s, and 30 s/3 min, which correspond to 28, 50, and 14.3% duty cycles, respectively. They found that all had similar seizure reductions and proportion of patients who responded at least 50%. However, the 30 s/3 min group had the earliest significant response and the highest number of 75% responders, so the authors concluded that it was likely the optimal ON/OFF for the initial 3 months (DeGiorgio et al., 2005).

Epilepsy is a clinical application of VNS that has a strong history and the convergent parameters are outlined in **Table 2**. There are several other studies included in the convergent parameters, however, not discussed in detail (Marrosu et al., 2003; Siddiqui et al., 2010; Marras et al., 2013; De Taeye et al., 2014; Fraschini et al., 2014; Orosz et al., 2014; Ryvlin et al., 2014; Boon et al., 2015).

VNS FOR TREATMENT RESISTANT DEPRESSION (TRD)

Vagus nerve stimulation as a treatment for depression followed FDA-approval for VNS for epilepsy. Much of the early research reported effects in patients who had VNS implants for epilepsy.

Elger et al. (2000) noted positive mood changes in prior VNS epilepsy trials, but with the caveat that it was difficult to identify whether mood changes were due to reduced seizures, improved quality of life, or some other reason. They designed a study that focused on this association within a larger randomized control trial for epilepsy. They measured eight psychiatric rating scales, two of which pertained to depressive mood and symptoms. They showed mood improvements that were independent of seizure improvement. The parameters used were like the "high" paradigm used in epilepsy: 500 μs, 30/300 s, 6 months duration, and maximum tolerability up to 1.75 mA (Elger et al., 2000).

That same year, a multicenter trial for VNS specific to treatment-resistant depression used parameters familiar by now: 500 μs, 20–30 Hz, and 30 s/5 min; the minor differences are that current was increased to a comfortable level, rather than the maximum level tolerable, and treatment lasted 10 weeks. They found that around 40% of subjects showed at least a 50% decrease in Hamilton Rating Scale for Depression (HRSD) scores, with similar results seen in other depression scales used in the secondary analysis (Rush et al., 2000).

Soon after, Bohning et al. (2001) devised a way to simultaneously activate VNS and capture fMRI. They demonstrated BOLD signals in regions associated with vagus afferent effects in several patients. They used a smaller but more rapid duty cycle (7 s ON, 108 s OFF, 6.1% cycle) than Elger et al. (2000) or Rush et al. (2000), but this is understandable given the different aims of the project (Bohning et al., 2001).

Mu et al. (2004) published the major parametric study for VNS as a depression treatment. They measured VNS effect with fMRI markers of depression and varied the pulse width (130, 250, or 500 μs) over three consecutive scans in twelve participants. They concluded that 250 and 500 μs had a greater association than 130 μs for global brain activation, while 130 and 250 μs had an association for global deactivation. The majority of the studies reviewed for the depression segment of this review used 500 μs.

Table 3 shows that many of the VNS for depression papers reviewed for this review share a common pulse width (500 μs) and ON/OFF time (30 s/5 min). There is evidence that VNS may aid depression treatment, but future work remains before widespread clinical use. There are several other studies examined in this section and referred to in the table but not discussed in detail (Sackeim et al., 2001; Lomarev et al., 2002; Mu et al., 2004; Nahas et al., 2005, 2007; Zobel et al., 2005; Conway et al., 2006, 2012; Pardo et al., 2008; Cristancho et al., 2011; Kosel et al., 2011; Aaronson et al., 2013; Hein et al., 2013; Fang et al., 2016; Rong et al., 2016; Perini et al., 2017; Tu et al., 2018).

FACILITATING NEUROPLASTICITY WITH VNS

One area of research that has grown rapidly in the past few years has examined the relationship of vagus afferents and

TABLE 2 | Human Epilepsy (Summary parameters of 19 studies).

	Pulse Width	Frequency	On/Off time	Time administered	Current
Most common Parameter	500 μs (10 uses)	30 Hz (9 uses)	30 s/5 min (7 uses)	No Common	No Common
Range of Parameters	130–500 μs	20 – 50 Hz	7–120 s ON/ 18 s – 60 min OFF	30 s – 24 mo	0.25–3.75 mA

TABLE 3 | Human Depression (Summary parameters of 20 studies).

	Pulse Width	Frequency	On/Off time	Time administered	Current
Most common Parameter	500 μs (12 uses)	20 Hz (13 uses)	30 s/5 min (9 uses)	6 mo (4 uses)	No Common
Range of Parameters	130–500 μs	1.5–30 Hz	7 s – 30 min ON/ 41–600 s OFF	14 min – 12 mo	0.13–6 mA

neuroplasticity. Many of these studies look at different kinds of injury repair, motor learning, memory, and hearing, and while this is not an all-inclusive list, we can assume that demonstrating plasticity in any of these domains has some generalizability to the others. We primarily will focus on VNS-paired behavioral interventions that rapidly accelerate learning, reorganize cortical networks, and facilitate recovery post-brain injury.

VNS-Paired Plasticity

Engineer et al. (2011) first paired VNS with tones and demonstrated that they could make targeted changes in A1 as measured by microelectrode mapping. They investigated whether VNS might have some use in tinnitus treatment. If over-represented frequencies can cause the disease, then increasing cortical representation of non-tinnitus tones may correct that imbalance. VNS paired with multiple tones had significant effects in behavioral testing and A1 responses in rat models (Engineer et al., 2011).

Another study used the same parameters but examined the rates of tone trains. Assuming from literature that rat A1 neurons typically respond to tones around 10 pulses per second, they paired VNS with more or less rapid trains. They showed that rapid pairing increased neuronal ability to follow rapid trains, while slow pairing decreased their ability to follow rapid trains (Shetake et al., 2012). When researchers paired rat VNS to speech sounds, A1 response increased to those sounds and not to novel speech sounds. The same parameters were used as the previous study (Engineer et al., 2015).

Pena et al. (2013) is one of many rat studies that have paired VNS to audio tones. Others would use tones as the stimulus alone instead of as conditioning. Researchers then examined the primary auditory cortex (A1) afterwards as a measurement of plasticity. Again, assuming that plasticity is a widespread underlying mechanism of VNS effects, findings in A1 are not in total isolation from findings in primary motor or somatosensory cortices. Many of them share VNS parameters (100 μs, 30 Hz, 500 m s train, and 0.8 mA), so there is a lot more comparability between these papers. An important concept to keep in mind for this section is the idea of tonotopy, or tone-mapping, in the auditory; peak response in areas of auditory cortex correspond to regions of the frequency spectrum.

Borland et al. (2016) investigated the question of whether current intensity affects VNS-paired plasticity. In their study, only current intensity was varied: they assigned rats to 0.4, 0.8, 1.2, or 1.6 mA for VNS paired with a given tone. After 20 days of paired stimulation they measured the area of A1 responsive to frequencies near the paired tone. 0.4 and 0.8 mA rats had significantly different area-response changes compared to control (naïve) rats, whereas the higher intensities failed to reach significance (Borland et al., 2016). This largely supports the effective level of current found in other studies, although it cannot directly support the inverted-U pattern.

The next parametric study used the same frequency, train length, and duration as the previous studies, but varied pulse width (100 or 500 μs) and current intensity (0.2 or 0.8 mA). They built on previous research that had repeatedly shown an inverted-U pattern for current intensity, as well as the levels of each that drove plasticity (100 μs and 0.8 mA). However, they designed this study to examine the relationship of pulse width and current. Starting from the customary parameters, dropping the current to 0.2 mA abolished the VNS benefits to plasticity. However, low current intensity (0.2 mA) with extended pulse width (500 μs) still had an effect, albeit less than the customary parameters. This suggests that there is interaction between these parameters. Furthermore, taken together with other research, they argued that shorter pulse width may have a permissive effect on current, in the sense that it allowed a wider range of currents to drive plasticity (Loerwald et al., 2018).

Recent research has also taken a closer look at the influence of timing on VNS and A1. Researchers varied the number of VNS-tone pairings and the amount of time that elapsed between them in acoustic trauma rat models. Inter-stimulus intervals correspond to OFF times; they found that shortened intervals (8 s instead of the standard 30 s) drove plasticity less than the standard protocol, while longer intervals (120 s) drove plasticity roughly as much as standard. Reducing the number of pairings (from the standard 300 pairings to only 50) abolished the plastic effects (Borland et al., 2018).

Functional Motor Improvements in Animals

Behaviorally, VNS paired rehabilitation showed produced functional improvement in motor tasks in rats with TBI. Researchers speculated about a "Norepinephrine hypothesis" so far suggested in VNS for epilepsy and memory might also apply to motor recovery. They used 500 μs pulses, 20 Hz frequency, 30 s ON, and 29.5 min OFF with current 0.5 mA and duration 14 days. Though the behavioral results were significant, they

found no histochemical differences. They also argued that their results supported the idea of plasticity in functional recovery (Smith et al., 2005).

Rats trained in a specific movement and paired it with VNS for 5 days showed a greater area of motor cortex responding to the paired (Porter et al., 2012). There are two important differences between these findings and Smith et al. (2005). First, whereas the previous paper used general motor tasks in injured rats, this paper focused on a specific movement in healthy ones. Second, Porter et al. (2012) used very different parameters because they cited them from Engineer et al. (2011) – an A1 plasticity paper (100 μs, 30 Hz, 500 m s train, and 0.8 mA). They argued that the mechanisms of plasticity may be similar in different areas of the brain, so a motor pairing should operate in the same way (Porter et al., 2012).

When researchers induced motor cortex ischemia in rats that they previously trained to a task, rats paired with VNS post-ischemia showed twice as much improvement compared to control. They cited Porter et al. (2012) and Engineer et al. (2011) for their parameters, though their treatment duration was longer than in either – 100 μs, 30 Hz, 500 m s train, 25 day, and 0.8 mA (Khodaparast et al., 2013).

Two studies by Seth Hays in 2014 (Hays et al., 2014a,b) used 30 Hz and 0.8 mA of current, similar to preceding animal studies in epilepsy. The timing of stimulation pulses was different on a few scales. The pulse width used was shorter (100 μs); this width is common in many rehabilitation and general plasticity experiments. Furthermore, the ON period was 500 ms triggered by movement, in contrast to the usual 30 s ON and regular OFF periods seen in epileptic studies. The irregular OFF period is because of a concept of paired timing in rehabilitation VNS and plasticity that VNS is effective in plasticity only when given in a very small window of time near the target function. Both studies demonstrated a significant improvement with VNS-paired rehabilitation and further confirm the importance of time-pairing the stimulus to action. They later confirmed this finding in aged rats (Hays et al., 2016). In rats with ischemic lesions, VNS not only augmented rehabilitation, but the effects lasted months after treatment ended, and carried some generalizable improvement to untrained tasks (Meyers et al., 2018). Impaired signaling of norepinephrine, serotonin, or acetylcholine can prevent the efficacy of VNS rehabilitation (Hulsey et al., 2019; Meyers et al., 2019). VNS also improved rehabilitation in cervical spine injury rats (Darrow et al., 2020b). There was benefit to somatosensory rehabilitation using similar parameters to those used by motor recovery experiments (Darrow et al., 2020a).

Implanted VNS for Adult Stroke Rehabilitation

The final portion of this section covers the limited research of VNS-paired rehabilitation in human subjects. A published protocol for a randomized crossover prospective clinical trial to find the effect of VNS-pairing in human subjects with traumatic brain injury (TBI) used the parametric ranges 10–30 Hz frequency and 0.5–2.5 mA current. Their pulse width and ON/OFF time resembled human VNS for epilepsy – 500 μs pulses for 30 s/5 min, respectively (Shi et al., 2013). However, contacting the senior author, it seems that the arrival of Hurricane Sandy prevented any follow-up on this paper.

A pilot randomized control trial studied VNS-paired rehabilitation in humans with ischemic stroke deficits in a pilot randomized control trial. 9 received VNS pairing and 11 received standard rehabilitation. Unlike the ranges used in Shi et al. (2013), the parameters they used over 6 weeks were identical to those used in rat plasticity research (100 μs pulse, 30 Hz, 500 m s train, and 0.8 mA). They found a significant improvement in upper extremity performance scores when analyzing the data per protocol, but not when analyzing it as intention-to-treat. It seems only one patient was lost from the control group between these two analyses for taking a medication that met exclusion criteria (Dawson et al., 2016).

An important case study on somatosensory rehabilitation in humans paired 5 weeks of the standard VNS plasticity parameters (100 μs, 30 Hz, 500 m s train, and 0.8 mA) with sensory training in a single human subject with deficits in the left arm. The subject improved over time in several measures of tactile sense. Though uncontrolled, it is worth noting that the stroke that caused the patient's symptoms happened 2 years previous, so it is difficult to imagine this recovery was spontaneous (Kilgard et al., 2018).

The next step was to compare VNS to a sham-VNS control. Researchers implanted VNS in 17 subjects (8 active, 9 sham) with upper extremity deficits following ischemic stroke. They showed that VNS-paired therapy patients had significantly more responders according to Fugl-Meyer Assessment – Upper Extremity (FMA-UE) scores, as well as significant long-term improvements in Wolf Motor Function tests. However, it is worth noting that several other motor assessments failed to show significant differences between the groups. The design of the rehabilitation is also important: each subject had a period of in-clinic therapy and at-home therapy, both of which delivered 500 ms of VNS at the standard 100 μs pulses, 30 Hz, and 0.8 mA. In the former (6 weeks), a therapist could assess the exercise and deliver VNS timed to each successful movement (500 ms train); in the latter (60 days), subjects were given a 30-min daily exercise regimen to do at home, at the start of which they would use a magnet to turn on the VNS for 30 min (500 ms ON every 10 s). There were not significant differences between group FMA-UE scores at the end of in-clinic therapy (Kimberley et al., 2018). Other studies in this section have highlighted the importance of timing in pairing, so it is possible that this design had some influence on the results. Recently, Dawson et al. (2021) completed the largest implanted VNS trial for motor rehabilitation that reliability demonstrates the efficacy of cervically implanted VNS to improve motor function when paired with post-stroke motor rehabilitation.

In conclusion, the field of VNS in plasticity may be one of the younger sub-fields, but parametrically it is one of the most consistent. In addition, it has studies optimizing almost every parameter.

TABLE 4 | Neuroplasticity and Rehabilitation (Summary parameters of 33 studies).

	Pulse Width	Frequency	On/Off time	Time administered	Current
Most common Parameter	100 μs (26 uses)	30 Hz (26 uses)	500 ms train (24 uses)	20 d and 6 w (6 uses)	0.8 mA (25 uses)
Range of Parameters	100–500 μs	7.5–120 Hz	500 ms – 30 s ON/ 29.5 s – 29.5 min OFF	30 s – 18 mo	0.2–3.2 mA

Plasticity is a consistent and strong field of VNS research that may shed light on many fundamental principles of neuroscience as a whole. There are several other studies examined in this section and **Table 4** but not discussed in detail (Clark et al., 1995, 1999; Bajbouj et al., 2007; Biggio et al., 2009; Vanneste et al., 2017; Buell et al., 2019; Hulsey et al., 2019; Meyers et al., 2019; Sanders et al., 2019; Darrow et al., 2020a,b).

TRANSCUTANEOUS AURICULAR VAGUS NERVE STIMULATION (TAVNS)

This new non-invasive form of VNS should consider the century of VNS literature to guide its administration. A note on literature conventions, however, it is important to note current is applied to the skin, rather than directly to the nerve. Here we will use taVNS to refer to all transcutaneous VNS acting on the ear (Badran et al., 2019; Farmer et al., 2020). This section is not intended to be an exhaustive review of all taVNS applications, however, we have chosen a representative pool of work from the rapidly growing field of neurological and psychiatric taVNS applications (Wang et al., 2021).

taVNS Human Parametric Studies

Ventureyra proposed the method underlying taVNS in 2000, combining the concepts of transcutaneous electrical stimulation of the nervous system (TENS), the anatomy of ear innervation, and research in acupuncture (Ventureyra, 2000). Later researchers applied this idea by running current through electrodes on several locations on the ear and measured significant vagus sensory evoked potentials from stimulation of the tragus. VSEP is measured from the scalp, so they could conclude that stimulation had an effect, but not exactly where or what (Fallgatter et al., 2003). So, while these results were promising, more work remained to determine whether this stimulation targeted areas associated with vagal afferents.

To our knowledge, the first parametrically relevant study stimulated the ear and recorded BOLD changes in fMRI, as well as pre- and post-psychometric assessments. As this was unbroken ground, they first ran a test series of several people to find the optimal stimulation parameters; however, they merely wrote that these were based on "ratings of quality of subjective perception," so it is unclear how rigorously they optimized the levels. Current intensity was set at perceptual threshold and just under pain threshold. They used 20 μs pulses, 8 Hz frequency, and ON/OFF time of 30 s/2 min (for psychometric tests) or 30 s/1 min (fMRI). Compared to sham, they found BOLD patterns like those seen in conventional VNS – decreased BOLD in limbic areas, increased BOLD in the thalamus, insula, and precentral gyrus. Psychometric scores showed significant subjective improvement of well-being in the taVNS group, whereas sham subjects saw worsening of subjective feelings (Kraus et al., 2007). Another fMRI study by this group validated these results using 20 μs, 8 Hz, 30 s/1 min cycles, and current just below pain threshold. In addition, they stimulated the anterior and posterior ear canal separately. Anterior and posterior stimulation both increased BOLD in the insula, but work in opposition in other areas; anterior canal stimulation decreased BOLD in the parahippocampus, posterior cingulate, and thalamus, while increasing BOLD in the locus coeruleus and solitary tract (Kraus et al., 2013). Lastly, a 2018 fMRI study further demonstrated the positive neurophysiological effects of supra-threshold taVNS delivered 500 μs, 25 Hz, in 30 s blocks when compared to sham using concurrent taVNS/fMRI (Badran et al., 2018b).

The taVNS field is still in its infancy, however, the literature thus far illustrates a diversity of other considerations in the parameters used. Current intensity is typically administered between perceptual and pain threshold – a dosing metric to control for pain as a confound. frequency often hovers between 20 and 30 Hz, but the other parameters vary without noticeable pattern. Badran et al. (2018) conducted a series of experiments that aimed to optimize taVNS using cardiac biomarkers. In back-to-back studies, they investigating varying pulse width and frequency while keeping current intensity standardized at 2 × perceptual threshold (Badran et al., 2018d). taVNS was administered during 1 h sessions, with ON/OFF 60 s/270 s (trial 1) or 60/150 s (trial 2). They varied frequency (1, 10, and 25 Hz) and pulse width (100, 200, and 500 μs) in nine combinations in the first trial, with a second trial using only the two best combinations from trial 1. They used heart rate change to measure the strength of vagus activation. Their results showed that 500 μs and 10 Hz had the strongest effect on heart rate, while 500 μs 25 Hz had the next strongest effect. Recall that most taVNS papers use 20–30 Hz frequency; while some have used 500 μs, it is far from a majority. They note that heart rate is an indirect way to assess the central effects of taVNS, so replication of these trials in imaging are needed in the future (Badran et al., 2018d). It will also have to be validated for different disciplines – for example, other research has found that 1 Hz was significantly better than 25 Hz at reducing headache frequency in chronic migraine patients (Straube et al., 2015).

Auricular neurostimulation introduces non-neural tissue between the electrodes and the nerve – which acts as an insulator and allows for further variation in parameters to be explored, including higher frequencies and intensities that may not be otherwise safely administered in animals without causing a lesion in the nerve. Without a consensus on ideal parameters, taVNS researchers carried on to human clinical trials, often

TABLE 5 | taVNS (Summary parameters of 22 studies).

	Pulse Width	Frequency	On/Off time	Time administered	Current
Most common Parameter	250 μs (5 uses)	25 Hz (12 uses)	30 s ON (9 uses but variable OFF)	No Common	Supra-Threshold (10 uses)
Range of Parameters	20–500 μs	1–30 Hz	0.5 s – 30 min ON / 30–270 s OFF	6 min – 9 mo	0.13–50 mA

using parameters similar to those administered in cervically implanted VNS analogs.

taVNS Human Clinical Trials

Following these functional imaging studies, taVNS began to emerge for a variety of different applications with widely divergent parameters. 2012 saw several pilot studies evaluating the feasibility of taVNS in different disease treatments. A single-armed pilot study applied taVNS for 3–10 weeks in patients with chronic tinnitus. They measured clinical electrocardiograms in clinical exams every few weeks. They found that taVNS was associated with possible QRS shortening. There were two adverse events, but the authors concluded that it was likely not due to stimulation. The researchers set taVNS parameters at 25 Hz, 30 s ON, 180 s OFF, and current between perceptual and pain threshold (approximate range 0.1–10 mA) (Kreuzer et al., 2012). Adverse events caused an early termination of the first phase, so they followed up with a second phase using a different stimulating device, 30 s ON/30 s OFF, and two fewer hours of stimulation per day. Altogether, the Kreuzer tinnitus work concluded safety, feasibility, significant changes from baseline for some clinical scores, but no decrease in clinical complaints (Kreuzer et al., 2014).

Other studies investigated the effect of taVNS in patients with resistant epilepsy. They applied taVNS for an hour three times daily for 9 months, and then recorded a week of video-EEG. Patients kept seizure diaries. Parameters used were 300 μs pulses, 10 Hz, 1 h ON, and current as high as the patients could tolerate regularly. They concluded that taVNS was safe and tolerable for long treatment courses, and five of the seven patients that completed the trial saw fewer seizures. However, the caveat to that tolerability is that three of the original ten subjects dropped out because the protocol was too much for them to do day-to-day, or for technical problems, or due to direct side effects (Stefan et al., 2012).

A full double-blind randomized clinical trial for taVNS in resistant epilepsy used different stimulation parameters: 250 μs, 25 Hz (or 1 Hz for the active control), ON/OFF 30 s/30 s, 20 weeks of treatment, and current set between perceptual and pain thresholds (average 1.02 mA control or 0.50 mA treated, with a statistically significant difference between the two). They showed that the treatment group that completed the treatment had a significant decrease in seizure frequency not seen in the control, but both groups had similar responder rates. They were unable to conclude that the 25 Hz was superior to the control (Bauer et al., 2016).

Two specific subsets of taVNS called Respiratory-gated Auricular Vagal Afferent Nerve Stimulation (RAVANS) (Garcia et al., 2017) and Motor Activated Auricular Vagus Nerve Stimulation (MAAVNS) (Cook et al., 2020a) emerged as closed loop solutions to the parametric problem. RAVANS works by the idea that inhalation induces transient inhibition of vagus nerve activity. Investigators have applied RAVANS to chronic pain subjects. The "ON" period is a train of 500 ms in response to exhalation, while the "OFF" period lasts until the start of the next expiration. They designed a counterbalanced crossover study for taVNS in patients with chronic pain in the pelvis and tested each patient with RAVANS or sham stimulation at least a week apart. Parameters were 450 μs pulses, 30 Hz, 30-min treatment sessions, and current set just below pain threshold. RAVANS has not only shown promise in treating pain disorders, but also other neurological disorders like migraine (Garcia et al., 2017). These studies suggest that taVNS effects are likely compounded by the respiration-induced vagal effects at the brain stem. MAAVNS, however, pairs taVNS with motor activity, using 500 μs pulses at 25 Hz that are turned on during the duration of a targeted motor activity (Cook et al., 2020b). MAAVNS has been demonstrated to be a promising neurorehabiltiation tool (Badran et al., 2018c, 2020) and in early studies has demonstrated promise in facilitating motor learning in neonates MAAVNS is further continued to be explored in adult post-stroke rehabilitation trials.

Further exploration of open-loop taVNS for pain control used forty-eight healthy subjects in a taVNS/sham crossover control. Their stimulation used 250 μs pulses at 25 Hz, 1 h ON, and current intensity between perceptual and pain thresholds (reported 0.25–10 mA). They cited Vonck et al. (1999), a study of conventional VNS in epilepsy, for the frequency. Their results showed some analgesic effects for mechanical pain and noxious heat (Busch et al., 2013).

Building upon all the promising animal and human implanted VNS work that has come out of Texas by groups led by Hays, Kilgard, and Engineer, many researchers have pushed taVNS into the motor rehabilitation space. Redgrave et al. (2018) conducted an open label pilot study using taVNS concurrently with post-stroke upper limb rehabilitation in 18 1-h sessions (25 Hz, 100 μs pulse width) with promising improvements in motor function. Baig et al. (2019) explored a similar post-stroke intervention as Redgrave, and demonstrated promising sensory recovery effects. Unlike Redgrave and Baig who used therapists to conduct the rehabilitation training, Capone et al. (2017) utilized robots to create a taVNS-paired robotic intervention for post-stroke rehabilitation. Lastly, the closed-loop, intelligent, MAAVNS system that has shown early success in neonates has been translated to adult upper limb rehabilitation and is being investigated in a small randomized trial (ClinicalTrials.gov Identifier: NCT04129242). This MAAVNS system delivers taVNS in a temporally specific fashion that builds upon the animal work described earlier in this manuscript.

In conclusion, ongoing work in taVNS may radically change the field and eliminate the barrier of surgery to many patient

populations. It is important to understand that aside from parametric considerations, taVNS is sensitive to stimulation target that, although is not discussed in this review (Badran et al., 2018). There are several other studies examined in this section and **Table 5** but not discussed in detail (Hein et al., 2013; Clancy et al., 2014; Capone et al., 2015; Frangos et al., 2015; Hasan et al., 2015; Fang et al., 2016; Rong et al., 2016; Yakunina et al., 2017; Badran et al., 2018b; Tu et al., 2018).

SUMMARY AND CONCLUSION

Vagus nerve stimulation is an important brain stimulation modality that has a history spanning over 150 years. Fascinatingly, there is still no consensus parameter that is the "best" parameter for VNS. There is likely no perfect combination of current intensity, pulse width, frequency, duty cycle, and duration - the more likely case is that there is a wide range of parameters that are biologically active and induce promising behavioral effects. Furthermore, there is an abundance of promising work that future research will uncover about the current-pulse width relationship in the plasticity field.

This manuscript is intended to serve as a historical perspective and guide future VNS trials and research. There are three key take home messages from this manuscript that we have synthesized below:

(a) Current intensity and pulse width are critical - From much of the work described in this manuscript, increasing current intensity gradually increases release of neurotransmitters like norepinephrine (Roosevelt et al., 2006; Follesa et al., 2007) and increasing firing rate of cells in the locus coeruleus (Hulsey et al., 2017). Many applications of implanted VNS titrate the intensity to comfort, and nearly all taVNS studies employ supra-threshold stimulation intensity.

The vagus nerve is a bundle of thousands of nerves, each with their own activation thresholds. The majority of these ascending fibers are small, unmyelinated C fibers, whereas the remaining are myelinated A and B fibers. A-beta fibers have the lowest firing threshold, which would be activated first, but not until higher current intensities are C fibers activated (Collins et al., 1960). The fundamentals of nerve conductance and firing thresholds should be considered in VNS, however, when directly stimulating the nerve, discomfort may impede the increasing of the intensity. Furthermore, the current intensity and pulse width interaction should be considered. When current intensities are equal, increasing pulse width allows for increased VNS effects (Loerwald et al., 2018). However, achieving higher current intensities may be only tolerable at lower pulse widths. This interaction needs to be further explored.

(b) Frequency seems to need less precision – In the review of these over 100 studies, it seems that the range of frequencies that have been carried onward over the years. Most manuscripts seem to settle on a frequency between 20–30 Hz, which has been shown to be more biologically active in both in implanted functional neuroimaging as well as in taVNS optimization trials. There has yet to be a broad parametric search for optimal frequency, however, the current state of the research suggests many of the behavioral effects are found in the range of the original anti-epileptic parameters of the early 1990's (Ben-Menachem et al., 1994b). There is a need to explore the systematic testing of varying frequency.

(c) On/Off times may be more state dependent than previously believed – much of the work described here explores a wide range of On/Off times, and mostly were employed early in VNS development to avoid lesions to the nerve and as a means to save battery life in the implant. The early work settled on 30 s ON, 5 min OFF, and not much has changed in the implant space. As we move to neuroplastic effects, ON/OFF times are less critical, and temporal pairing of stimulation bursts with behavioral interventions was more effective (Hays et al., 2014a). As we move to taVNS, safety and power issues of the implanted VNS have been resolved as external pulse generators can be easily recharged and stimulation is not delivered directly to the nerve. Pairing of taVNS with behaviors is also emerging as shown in both the RAVANS (Garcia et al., 2017) and MAAVNS (Cook et al., 2020b) applications.

As VNS research grows, we should consider the historical perspective and further optimize the parameter space. There is room for improvement and a large body of literature that can be improved upon as VNS continues to emerge as a promising neuromodulation modality.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Use of Transcutaneous Auricular Vagus Nerve Stimulation as an Adjuvant Therapy for the Depressive Symptoms of COVID-19: A Literature Review

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The coronavirus disease 2019 (COVID-19) comprises more than just severe acute respiratory syndrome. It also interacts with the cardiovascular, nervous, renal, and immune systems at multiple levels, increasing morbidity in patients with underlying cardiometabolic conditions and inducing myocardial injury or dysfunction. Transcutaneous auricular vagus nerve stimulation (taVNS), which is derived from auricular acupuncture, has become a popular therapy that is increasingly accessible to the general public in modern China. Here, we begin by outlining the historical background of taVNS, and then describe important links between dysfunction in proinflammatory cytokine release and related multiorgan damage in COVID-19. Furthermore, we emphasize the important relationships between proinflammatory cytokines and depressive symptoms. Finally, we discuss how taVNS improves immune function via the cholinergic anti-inflammatory pathway and modulates brain circuits via the hypothalamic–pituitary–adrenal axis, making taVNS an important treatment for depressive symptoms on post-COVID-19 sequelae. Our review suggests that the link between anti-inflammatory processes and brain circuits could be a potential target for treating COVID-19-related multiorgan damage, as well as depressive symptoms using taVNS.

Keywords: transcutaneous auricular vagus nerve stimulation, COVID-19, brain circuits, depression, epidemic

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BACKGROUND

In December 2019, a novel coronavirus disease (COVID-19) outbreak emerged from Wuhan, Hubei Province, China, initiating a global health threat and posing a challenge to the psychological resilience of populations worldwide (1). Clinically, presentation of COVID-19 varies from being asymptomatic, to including mild symptoms such as fever, sore throat, headache, fatigue, to manifesting as severe acute respiratory distress syndrome (ARDS) (2). Moreover, it also interacts with the cardiovascular, nervous, renal, and immune systems at multiple levels (3). An extreme immune reaction resulting in elevated levels of inflammatory cytokines, often

referred to as a cytokine storm, has been linked to an increased number of deaths from COVID-19 (4, 5). However, even worse than this, the COVID-19 pandemic has also led to an increased prevalence of mental health problems, such as difficulty sleeping, depression and anxiety, and hypomania (6). Although a number of vaccines have been proved to be effective (7, 8), evidence-based evaluations and interventions targeting mental health disorders are relatively scarce (9). Transcutaneous auricular vagus nerve stimulation (taVNS) is being explored as an adjuvant therapy to the depressive symptoms of COVID-19 during the pandemic to deal with these disorders.

The concept of taVNS as a therapy has emerged relatively recently. The technique makes use of the analgesic effects of the neuronal network that innervates the vagus nerve (10), which targets the cutaneous receptive field of the auricular branch of the vagus nerve at the outer ear (11). Promising results indicate that, following taVNS treatment, the symptoms of mood disorders can be alleviated painlessly and without the need for surgery (12). Ventureyra was the first to propose applying vagus nerve stimulation (VNS) using surgically implanted electrodes wrapped around the vagus nerve in the neck (10). In 2005, VNS was approved as a long-term adjunctive treatment for patients with refractory depression of more than 18 years of age (13, 14). From a neuroanatomical point of view, vagus nerve fibers project to the nucleus tractus solitarius (NTS) and the locus coeruleus (LC), where they form direct and indirect ascending projections to many brain regions, including the midbrain, hypothalamus, amygdala, hippocampus, and frontal lobe (15). The vagus nerve, which is the longest nerve in the body, connects the central nervous system to the body by innervating major visceral organs such as the liver, spleen, and gastrointestinal tract (16). Once an inflammatory response has been detected, taVNS may help to attenuate inflammatory responses via the cholinergic anti-inflammatory pathway and by modulating brain circuits via the hypothalamic–pituitary–adrenal (HPA) axis (3, 17). Acute respiratory distress syndrome (ARDS) or fulminant pneumonia can lead to widespread inflammation and very high concentrations of cytokines in the lungs, accompanied by activation of the anti-inflammatory pathways mentioned above (18). To date, clinical and laboratory research demonstrated that taVNS can improve lung function (19, 20). In addition, taVNS is commonly used to treat encephalopathy, encephalitis, ischemic infarcts, cerebral venous thrombosis, as well as peripheral nervous system pathologies [i.e., muscle injuries, and peripheral neuropathies; (21–26)].

Abbreviations: ACh, acetylcholine; AMY, amygdala; ARDS, acute respiratory distress syndrome; BA, Brodmann areas; CCL-2, C-C motif chemokine ligand; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; EN, epinephrine; fMRI, functional magnetic resonance imaging; GC, glucocorticoid; HIP, hippocampus; HPA, hypothalamic pituitary adrenal; IL, interleukin; IL-1ra, interleukin-1 receptor antagonist; LC, locus coeruleus; MDD, major depressive disorder; MH, medial hypothalamus; mPFC, medial prefrontal cortex; MRS, magnetic resonance spectroscopy; NAc, nucleus accumbens; NE, noradrenaline; NTS, nucleus tractus solitarius; PFC, prefrontal cortex; PTSD, post-traumatic stress disorder; rACC, rostral anterior cingulate cortex; taVNS, transcutaneous auricular vagus nerve stimulation; TCM, Traditional Chinese Medicine; TNF, tumor necrosis factor; vmPFC, ventromedial prefrontal cortex; VNS, vagus nerve stimulation.

In order to better understand the mechanisms underlying taVNS, we review the literature on proinflammatory cytokines and the brain imaging correlates of taVNS. To date, there have not been any reviews that considered in detail how taVNS might treat depressive symptoms, which develops from COVID-19, or its associated co-morbidities. We provide an integrated account of how the dysregulation of inflammatory and immunological responses affect brain circuits in COVID-19.

HISTORICAL BACKGROUND OF taVNS

Auricular acupuncture originated in China during the Chou period (first millennium BCE) and has recently attracted scientific and public attention as it becomes increasingly accessible to the general public in modern China (**Figure 1A**) (28). The practice of auricular acupuncture is referenced in the Huangdi Neijing (The Yellow Emperor's Classics of Internal Medicine), which describes how the ear is not isolated but rather is directly or indirectly connected with 12 meridians (six yang and six yin) (29). In the 1950s, Dr. Paul Nogier, a French neurologist, proposed that the outer ear represents "an inverted fetus map" (**Figure 1B**) (30)]. In 1990, the World Health Organization (WHO) recognized auricular acupuncture as a self-contained microacupuncture system that maps all portions of the ear to specific parts of the body and to the internal organs (31). Having considered the anatomy of the neural pathways in the external auricle, Usichenko et al. proposed that the analgesic effects of auricular acupuncture could be explained by stimulation of the auricular branch of the vagus nerve (32). The vagus is known to be a mixed nerve, with about 80% of its fibers carrying sensory afferent information to the brain and about 20% carrying efferent motor information to the liver, spleen, and gastrointestinal tract (33). Thus, it is very likely that taVNS functions based on the Chinese system of energy circulation along the meridians, which connect "diseased" body organs with the external auricle. In addition to Asian countries, in which this technique is widely available and easy to apply, it may be possible to use taVNS to effectively respond to the COVID-19 pandemic-related depressive symptoms as well as multiorgan damage in environments where medical resources are limited.

THE IMPORTANT LINK BETWEEN PROINFLAMMATORY CYTOKINES AND COVID-19 PANDEMIC-RELATED MULTIORGAN DAMAGE

Several studies have suggested that the pathogenesis of COVID-19 involves an inability to resolve the inflammatory response along with the activation of immune cells and inflammatory cytokines (18, 34). In COVID-19 patients, an unregulated inflammatory response to the infection can result in the dysregulation of T cells with associated lymphopenia, high levels of the proinflammatory cytokines interleukin (IL)-6 and tumor necrosis factor (TNF)-α, and high levels of inflammatory chemokines, including C-C motif chemokine ligand (CCL-2) (35). In a study by Staats et al., 49-year-old man with

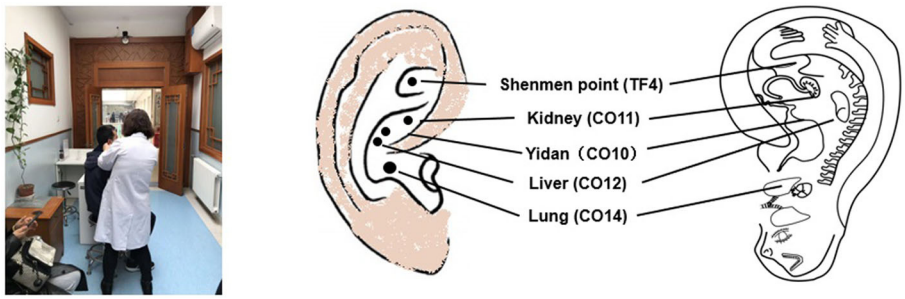

FIGURE 1 | (A) Auricular acupuncture practice has recently been attracting the attention of the public in China and is commonly carried out within the Chinese medical hospital system. **(B)** TF4 and CO10-12 are used to stimulate the auricular branch of the vagus nerve, with the outer ear corresponding to an "inverted fetus map" [according to King and Hickey, 2013 (27)].

excessive fatigue, mental cloudiness and body aches, and mental cloudiness had ceased after 5 days non-invasive VNS therapy (19). Furthermore, the authors also summarized five studies that used taVNS to treat COVID-19 and reported that the majority of patients obtain relief from respiratory distress after taVNS therapy. Three review papers have hypothesized that the cytokine storm and the worsening of patient health can be ameliorated or even prevented by taVNS (3, 18, 36). Therefore, targeting the inflammatory response and immune cells using taVNS might be a promising line of research in the fight against COVID-19-related inflammatory cytokine-induced multiorgan damage.

Current research indicates that COVID-19 might involve multiple organs including those in the central and peripheral nervous systems, rather than being restricted to the respiratory system (37). Recently, it has been noted that COVID-19 patients experience a number of different neurological symptoms, such as headache, dizziness, hyposmia, and hypogeusia during the course of the illness (38). Psychiatric symptoms, including post-traumatic stress disorder (PTSD), anxiety, and depressive symptoms, have also been reported in patients with COVID-19 (39, 40). Even worse than this, Kremer et al. found signal abnormalities in the medial temporal lobe and non-confluent multifocal white matter hyperintense lesions (41). Post-mortem brain imaging has demonstrated subcortical hemorrhagic and cortico-subcortical edematous changes, as well as olfactory impairment in patients who died of COVID-19 (42). Based on the results of published studies, COVID-19 encephalopathy appears to be more common in cases comorbid for encephalopathy, encephalitis, acute disseminated encephalomyelitis, myelitis, meningitis, ischemic infarcts, or cerebral venous thrombosis (43). In the peripheral nervous system, COVID-19 has been associated with dysfunction in the sense of smell and taste, and with muscle injury (41). Of note, the etiology of the encephalopathy in COVID-19 mentioned above is mostly linked to injury of the central and peripheral nervous systems by a cytokine storm, blood clots, or direct damage to specific receptors (41, 44). The pathogen that causes COVID-19, severe acute respiratory syndrome coronavirus 2, can invade the brain via vascular, peripheral nervous, lymphatic, cerebrospinal fluid pathways (45).

THE IMPORTANT LINK BETWEEN PROINFLAMMATORY CYTOKINES AND DEPRESSIVE SYMPTOMS

Several studies have suggested that inflammation or immune dysregulation are implicated in the pathophysiology of depression (46–51). It is now well-established that both the innate and adaptive immune systems become dysregulated in depressed patients and that controlling inflammation might be of therapeutic benefit (52). Two meta-analyses showed reliably higher levels of inflammatory markers in depression, namely IL-1β, IL-6, C-reactive protein (CRP), and TNF-α (53, 54). Plasma CRP in depression was not only positively associated with plasma levels of inflammatory cytokines (e.g., IL-6, TNF-α, sTNFR2, and IL-1ra), but also correlated with the level of CRP in cerebrospinal fluid (55). Both Alexopoulos et al. and Galecki et al. reported continual interactions between changes in the peripheral immune response and central immune activation [e.g., macrophage accumulation and microglial activation; (56, 57)]. These central and peripheral immune changes lead to increased production of proinflammatory cytokines (58, 59), which in turn lead to abnormalities in brain circuits. To some extent, this permits the relationship between abnormalities in brain circuits and inflammatory states in depression to be inferred. Hao et al. demonstrated that psychiatric patients were significantly higher in their levels of worry, anger, impulsivity, and intense suicidal ideation than healthy controls during the peak of the COVID-19 epidemic (60). Based on the psychological impact of the COVID-19 pandemic on psychiatric patients, targeting the cholinergic anti-inflammatory pathway and modulating brain circuits using taVNS is a rational approach to treating COVID-19 and its associated cytokine storm. Controlling inflammation might provide an overall therapeutic benefit, regardless of whether it is secondary to early life trauma, a more acute stress response, microbiome alterations, a genetic diathesis, or a combination of these and other factors.

DYSFUNCTION OF CORTICO-LIMBIC-STRIATAL CIRCUITS IN DEPRESSION

Dysfunction of the cortico-limbic-striatal neural system, including cortical (anterior cingulate and prefrontal cortex) and limbic (amygdala, hippocampus, parahippocampal gyrus, cingulate gyrus, nucleus accumbens, and striatum) areas has been implicated in depression (61–63). Mayberg found dorsal and lateral cortical hypoactivity and ventral limbic hyperactivity in depression using positron emission tomography (64). Taylor and Liberzon also proposed a hypo-dorsal and -lateral cortical model of cognitive processes and a hyper-limbic model of emotional expression to account for the experience of depression (65). Using tasks requiring executive control and emotional information processing, Siegle et al. identified sustained increased amygdala activity in response to emotional information processing and decreased dorsal prefrontal cortex activity in response to executive cognitive tasks (66). Using a meta-analytic technique, Fitzgerald et al. identified two neural systems implicated in emotional regulation in depression, including reduced activity in dorsolateral prefrontal cortex and more dorsal regions of the anterior cingulate cortex (67). Furthermore, they found increased activity in medial prefrontal cortex and in subcortical regions related to emotional processing in the depressed state. All of these changes returned to normal after antidepressant treatment. Together, these studies imply that patients with depression may exhibit impairments in their cognitive control network, as evidenced by their inability to disengage from negative stimuli (68). In addition, they show impairments in their affective control network, as evidenced by the hyperactivity of their amygdala and hippocampus to negative stimuli and recall.

THE STIMULATION LOCATION OF taVNS

Discrepancies in stimulation locations exist among studies that stimulated the auricular branch of the vagus nerve (69). The location is often dictated by the geometry of an electrode, with clip electrodes typically attached to the tragus or cymba concha (70–73). The outer auditory canal is also reported as a stimulation site, without further clarification for the electrode location (74–76). Based on Peuker and Filler's anatomical studies, the auricular branch of the vagus nerve innervates the tragus, concha, and cymba concha (77). However, it is difficult to select an optimal stimulation site for any particular disorder. The taVNS devices are relatively inexpensive, small, and mobile, which will be performed at patient's home after training (78).

STIMULATION PARAMETERS FOR taVNS

As taVNS is a novel treatment, there is currently no consensus on the appropriate stimulation parameters for its therapeutic use. According to the latest published International Consensus on taVNS (79), the points stimulated by taVNS are located in the auricular concha region, which contains a rich distribution of vagus nerve branches. Stimulation parameters used in taVNS studies have included: (1) a 20-Hz continuous sinusoidal wave (wave width, 0.2 ms) (80, 81); a 10-Hz continuous sinusoidal wave (73); a 20–30 Hz continuous sinusoidal wave (82, 83); a 4/20 Hz dense wave (between 0.8 and 1.5 mA) (84); a 20 Hz dense wave (between 4 and 6 mA) (72, 85); 1.5 Hz unipolar rectangular waves (0–600 mA) (69); a 120 Hz pulse wave (12 mA) (86); a 25 Hz monophasic rectangular waves (87); and (2) a gradually increasing stimulation intensity, starting from zero up to the highest point that the patients could tolerate (typically between 4 and 6 mA) (12). In terms of the safety of taVNS, a systematic review by Redgrave et al. reported the side effects of taVNS as local skin irritation, headache, nasopharyngitis, and a number of potentially serious adverse events [e.g., palpitations; (88)]. Indeed, the vagus nerve projects to the parabrachial nucleus, which can regulate heart rate, with one study showing that taVNS can cause side effects on heart rate when specific stimulation parameters (pulse width, 500 μs; frequency, 25 Hz) are used (89). However, in most cases, side effects were not apparent or disappeared after follow up (86, 90, 91).

GENDER AND AGE-DEPENDENT DIFFERENCES FOR taVNS

VNS has greater effects in females in animal studies, probably because of the effect of estrogens on muscarinic acetylcholine receptors in the central nervous system (92). Similar effects would be expected in females human subjects due to both hormonal levels and the gender-dependent differences in the functions of the autonomic nervous system (93, 94). Age is associated with marked changes at the hormonal level, which in turn affect acetylcholine-mediated parasympathetic autonomic activity (95, 96). Fallgatter et al. reported that the vagus sensory-evoked potentials showed a trend toward reduction in the elderly, associated with age-related demyelination of neuronal structures or degenerative processes (97). In addition, sensitivity to electrical transcutaneous stimulation was found to be lower in the elderly (98).

THE RELATIONSHIP BETWEEN PROINFLAMMATORY CYTOKINES AND BRAIN CIRCUITS IN DEPRESSION

There is now accumulating evidence that different forms of proinflammatory cytokine-mediated communication between the immune system and brain circuits modulate the inflammatory pathway in the brain (99–101). Rodent and human neuroimaging studies combined with experimental inflammatory challenges have been successful in clarifying the sensitivity of the insula and striatum to changes in peripheral inflammation in depression (102). Of note, neuroinflammation is associated with structural and functional anomalies in depression (103). A negative correlation was found between CRP levels and the cortical thickness of the right medial prefrontal cortex (mPFC) in depression (104). In a recent resting-state functional magnetic resonance imaging (fMRI) study, CRP

level was negatively correlated with amygdala–ventromedial prefrontal cortex (vmPFC) connectivity in depressed patients with high levels of inflammation and symptoms of anxiety (105). Haroon et al. demonstrated that plasma CRP levels are significantly associated with glutamate levels in the left basal ganglia using magnetic resonance spectroscopy (MRS) (106), and increased glutamate in the left basal ganglia in turn correlated with anhedonia and psychomotor slowing. Haroon et al. further pointed out that patients with high levels of both inflammation and basal ganglia glutamate showed decreased local homogeneity in vmPFC, and in dorsal and ventral striatal regions (107). In their study of medically stable patients with depression, Felger et al. reported that levels of CRP, as well as those of IL-6, IL-1beta, and IL-1ra, were negatively associated with connectivity between ventral striatum and vmPFC, and that this decreased connectivity in turn correlated with increased anhedonia (108). Moreover, the level of CRP was negatively correlated with connectivity between dorsal striatum, vmPFC, and presupplementary motor area. Decreased connectivity between dorsal striatum, vmPFC, and presupplementary motor area were further correlated with motor speed and psychomotor slowing. More recently developed methods, such as large-scale network-based analyses, were used by Yin et al. to show that the increased level of CRP is associated with reduced connectivity in ventral striatum, amygdala, orbitofrontal and insular cortices, and posterior cingulate cortex (109). Using surface-based morphometry, Kakeda et al. demonstrated that cortical thicknesses, such as those of the superior frontal and medial orbitofrontal cortex, showed a significant inverse correlation with the level of IL-6 (110). Using automated cortical parcellation within the mPFC including Brodmann areas (BA) 9, 10, 11, 24, 25, and 32, Meier et al. found an inverse relationship between plasma CRP level and the thickness of BA32, with recurrent MDD patients having a thinner cortex in BA32 (104). Using voxel-based morphometry, Chen et al. found that orbitofrontal cortex, lingual gyrus, inferior frontal cortex, middle frontal cortex, and planum polare were negatively correlated with levels of IL-6 (111). Moreover, Frodl et al. reported an inverse relationship of IL-6 concentration and hippocampal volume in MDD (112). Doolin et al. provided additional evidence to support a negative association between CRP levels and hippocampal subfield volumes (113). Importantly, the striatum, vmPFC, and presupplementary motor area are part of the classical reward and motor circuitry that receives neurotransmitters such as glutamate, in addition to dopaminergic innervation (114–116). Furthermore, Nusslock et al. found that higher levels of inflammatory biomarkers (e.g., CRP, IL-6, IL-10, and TNF-α) were associated with lower connectivities within both the emotional network and the central executive network in urban African American youths, suggesting that inflammation or neuroimmunology may be involved in the pathogenesis of emotional and physical health problems (117). More importantly, Cosgrove et al. reported that higher levels of CRP were related to greater coupling of orbitofrontal cortical and anterior insular activity with increased appetite in depressed patients (118). Together, these studies imply that systemic low-grade inflammation is associated with the coupling of activity in striatum with that in reward- and interoceptive-related neural circuitry, and provide evidence for physiological subtypes within depression.

EFFECTS OF taVNS ON THE LIMBIC-CORTICO-STRIATAL-THALAMO-CORTICAL CIRCUITS TO ADDRESS THE DEPRESSIVE SYMPTOMS OF COVID-19

Macrophages, proinflammatory cytokines (such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α) and chemokines released by respiratory epithelial and dendritic cells, are all known to play a role in the pathogenesis of critical patients with COVID-19 (119). Consequently, Bonaz et al. hypothesized that targeting the cholinergic anti-inflammatory pathway by vagus nerve stimulation could be a useful therapeutic option for patients with COVID-19. In support of this hypothesis, Staats et al. recently reported two patients with respiratory symptoms that were similar to those associated with COVID-19 who showed marked clinical benefit following the application of transcutaneous cervical vagus nerve stimulation (19). Research has also shown that the levels of proinflammatory cytokines, including IL-6, IL-10, IL-12, IL-13, and TNF-α, are elevated in MDD when compared to those of healthy controls (120). However, there is still a clear shortage of evidence supporting the neuroimaging findings of taVNS in the treatment of depressive symptoms in patients with COVID-19. Our previous review has validated taVNS may inhibit both peripheral and central inflammation and modulate multiple neural systems (121). Studies have demonstrated that taVNS increases connectivity of the nucleus accumbens (NAc) with bilateral mPFC/rostral anterior cingulate cortex (rACC); NAc with insula, occipital gyrus, and lingual/fusiform gyrus; amygdala with dorsolateral prefrontal cortex; and the default mode network (DMN) with precuneus and orbital prefrontal cortex. In addition, studies have reported decreased connectivity of medial hypothalamus (MH) with rACC, and DMN with anterior insula and parahippocampus (72, 85, 122, 123). Therefore, we argued that it was advantageous for treating the inflammatory processes associated with COVID-19 and modulate brain activity in the NAc, hypothalamus, DMN, amygdala, and rACC via the auricular branch of the vagus nerve (78). Further, it has been suggested that taVNS can attenuate inflammation by targeting the HPA axis (16).

Finally, since the beginning of the COVID-19 pandemic, various manifold neuroimaging features have been described for patients with COVID-19 and a range of interesting and helpful findings have been described across the globe (124). For example, Jain et al. found that acute stroke was the most common finding on neuroimaging; 92.5% of patients with positive neuroimaging studies also showed evidence of acute stroke on neuroimaging. Acute stroke is therefore a strong prognostic marker for a poor outcome (125). In another study, Mao et al. reported that 36.4% of patients had headache, dizziness, impaired consciousness, acute cerebrovascular disease, ataxia, and seizures, and that 8.9% of patients experienced specific manifestations in their senses,

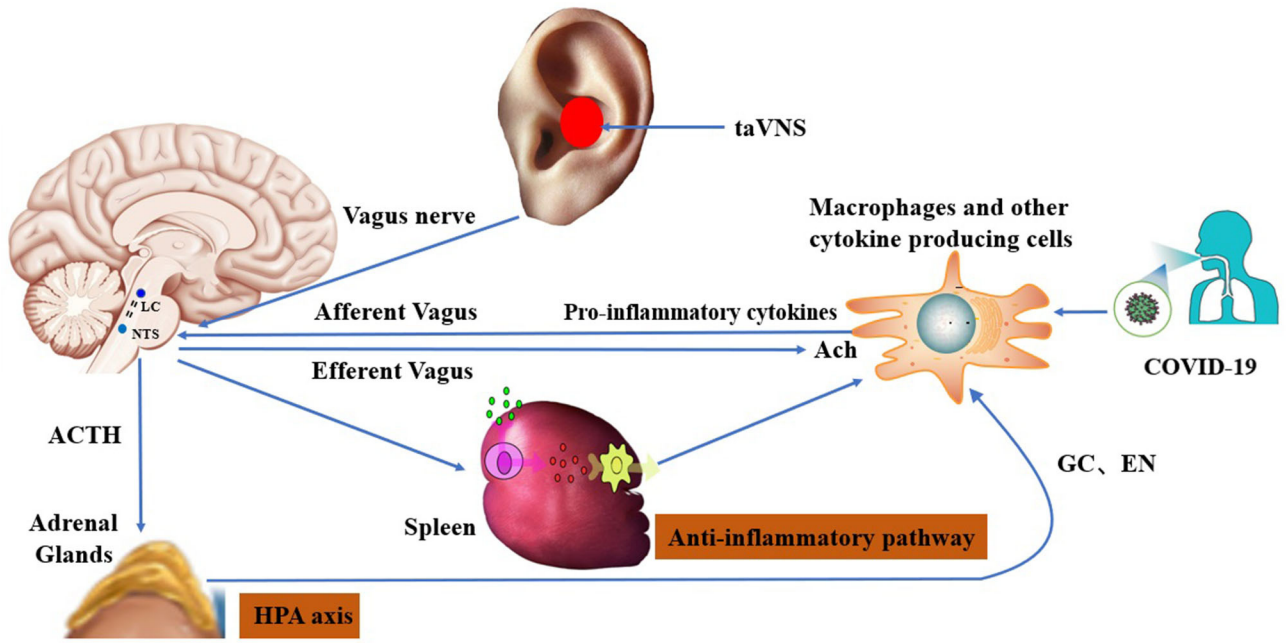

FIGURE 2 | Hypothesized mechanisms of transcutaneous auricular vagus nerve stimulation in the treatment of post-COVID-19 sequelae: 1) improvement in immune function via the cholinergic anti-inflammatory pathway; and 2) modulation of brain circuits via the HPA axis [according to Bonaz and Sinniger, 2016 (134)].

including taste, smell, vision impairment, and nerve pain (126). Furthermore, Brouwer et al. reported that acute cerebrovascular events were also detected in ∼3% of patients and that 6% of patients with severe manifestations had cerebrovascular events (127). Similarly, Tsai et al. reported a wide range of neurological manifestations, including olfactory taste disorders, headache, acute cerebral vascular disease, dizziness, altered mental status, seizure, encephalitis, neuralgia, ataxia, Guillain-Barre syndrome, Miller Fisher syndrome, intracerebral hemorrhage, polyneuritis, and dystonic posture (128). In addition, Al-Olama et al. reported that COVID-19 infection can cause meningoencephalitis in right frontal intracerebral hematomas, subarachnoid hemorrhage, and in frontal and temporal lobe thin subdural hematomas (129). Therefore, obtaining detailed neurological examinations and neuroimaging for the early and accurate diagnosis of these often fatal neurological complications could significantly improve our understanding of COVID-19 and its neurological manifestations.

EFFECTS OF taVNS ON THE CHOLINERGIC ANTI-INFLAMMATORY PATHWAY AND HPA AXIS

The cholinergic anti-inflammatory pathway via the vagus nerve has been proposed to be a key mediator of cross-communication between the peripheral immune system and the brain (130). Indeed, an increase of TNF-α in the liver and blood induced by an extreme immune reaction or cytokine storm was successfully dampened by stimulation of the vagus nerve, inducing an anti-inflammatory effect involving the release of acetylcholine (ACh) (131). Promisingly, Staats et al. reported clinically meaningful benefits of VNS in two COVID-19 patients with severe acute respiratory syndrome (19). The vagus nerve has a dual anti-inflammatory role, with 80% of the afferents targeting the cholinergic anti-inflammatory pathway and 20% of efferent fibers targeting the HPA axis (132). The efferent fibers of the vagus nerve activate the HPA axis, causing glucocorticoid release from the adrenal glands (133). Efferent fibers also run through the neck, connecting the brainstem to many organs, including the spleen, where they inhibit the release of TNF-α (16). Targeting the vagus nerve non-invasively may open up novel adjuvant approaches to treating COVID-19 patients. The various mechanisms by which taVNS may treat inflammation and related organ dysfunction in COVID-19 are illustrated in **Figure 2**.

TRADITIONAL CHINESE MEDICINE (TCM) ON COVID-19

TCM has a history of more than 2,000 years in the prevention and treatment of epidemics and plagues and the national health commission of China has recommended some patent Chinese medicine, such as Jinhua Qinggan granules, Lianhua Qingwen capsules, Xuebijing injections, a Qingfei Paidu decoction, a Huashi Baidu decoction, and a Xuanfei Baidu decoction (135). Patients with COVID-19 who took Jinhua Qinggan granules recovered faster than those who did not take the granules (136). Therapeutic efficacy was significantly higher in patients with COVID-19 taking Lianhua Qingwen capsules and Arbidol

(umifenovir) than that in those taking Arbidol alone; moreover, the conversion rate to severe disease in patients taking these capsules was significantly lower than that in patients taking Arbidol alone (137). Furthermore, chest computed tomography images of patients with COVID-19 showed improvement after 6 days of treatment with Qingfei Paidu decoction (138). In addition, other therapies such as acupuncture might also play a beneficial role in treating breathlessness after COVID-19 (4). Thus, TCM could play an important role in fighting COVID-19 in China.

CONCLUSIONS

This review has provided a comprehensive evaluation of targets for taVNS that can be used to treat inflammation and related organ dysfunction in COVID-19. It is clear that COVID-19 involves interrelationships between proinflammatory cytokines and brain circuits. The research findings detailed here suggest that taVNS could be used as an adjuvant therapy for depressive symptoms during the COVID-19 pandemic. We present a rationale for targeting the anti-inflammatory process and modulating brain circuits to treat COVID-19 and its associated cytokine storm. The evidence we present suggests that in theory, in response to the respiratory symptoms and immune system damage caused by COVID-19, taVNS can be used to improve immune function and may be an important treatment for depressive symptoms on post-COVID-19 sequelae. We describe the multi-level mechanisms linking taVNS and regulation of systemic anti-inflammatory responses and prevention of neuroinflammation present so as to treat depressive symptoms during the COVID-19 pandemic. When pro-inflammatory cytokines are present due to an infection, taVNS can activate afferent vagal neurons through impacting the immune response (139, 140) and also efferent vagal neurons can release acetylcholine through the cholinergic anti-inflammatory pathway and HPA axis (132, 141). Then, we summarize how applying taVNS and targeting cognitive and mental distress through influencing the connectivity of neural networks (121). taVNS has been shown to be associated with improved the default mode network functioning, which has been implicated in cognitive as well as emotional functioning (72, 142). Further studies are needed to understand the relationship between the immune system and the brain, as well as the role of taVNS.

AUTHOR CONTRIBUTIONS

This paper was primarily written by C-HL, PS, and Z-PG. Figures were produced by C-HL, Z-PG, Z-QZ, DL, and M-HY. All authors read and approved the final manuscript.

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