REVIEW

The potential role of vagus-nerve stimulation in the treatment of HIV-associated depression: a review of literature

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Abstract: Depression is the most common comorbidity and neuropsychiatric complication in HIV. Estimates suggest that the prevalence rate for depression among HIV-infected individuals is three times that of the general population. The association between HIV and clinical depression is complex; however, chronic activation of inflammatory mechanisms, which disrupt central nervous system (CNS) function, may contribute to this association. Disruptions in CNS function can result in cognitive disorders, social withdrawal, fatigue, apathy, psychomotor impairment, and sleep disturbances, which are common manifestations in depression and HIV alike. Interestingly, the parasympathetic system-associated vagus nerve (VN) has primary homeostatic properties that restore CNS function following a stress or inflammatory response. Unfortunately, about 30% of adults with HIV are resistant to standard psychotherapeutic and psychopharmacological treatments for depression, thus suggesting the need for alternative treatment approaches. VN stimulation (VNS) and its benefits as a treatment for depression have been well documented, but remain unexplored in the HIV population. Historically, VNS has been delivered using a surgically implanted device; however, transcutanous VNS (tVNS) with nonsurgical auricular technology is now available. Although it currently lacks Food and Drug Administration approval in the US, evidence suggests several advantages of tVNS, including a reduced side-effect profile when compared to standard treatments and comparable results to implantable VNS in treating depression. Therefore, tVNS could offer an alternative for managing depression in HIV via regulating CNS function; moreover, tVNS may be useful for treatment of other symptoms common in HIV. From this, implications for nursing research and practice are provided.

Keywords: tVNS, depression, HIV, vagus nerve

Introduction

Depression is the most common comorbidity and neuropsychiatric complication in HIV-positive adults, with an occurrence rate of approximately 40%–60% over a lifetime. Moreover, estimates suggest that the prevalence rate for depression among HIV-infected individuals is three to four times that of the general population.[1–3] Approximately 55%–65% of adults with HIV treated for depression experience a reduction in depressive symptoms.[4] However, as many as 30% of adults with HIV-associated depression are resistant to standard treatments (eg, psychopharmacology and psychotherapy), suggesting the need for alternative treatment approaches. As such, novel technologies should be explored for use in this population.

The association between HIV and clinical depression is complex. Chronic activation of stress mechanisms that disrupt central nervous system (CNS) function likely drives

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this association, as both conditions present with pathological proinflammatory states. According to Kim et al,[5] a significant relationship exists between depression and increases in proinflammatory cytokines (such as IL6, IL1β, TNFα, and CRP); moreover, severity of depression is correlated with reductions in BDNF. Likewise, proinflammatory cytokines and reduced BDNF have been associated with the progression of HIV and its associated neurocognitive disorders.[6,7]

Comorbid depression in HIV reduces antiretroviral medication adherence, which independently leads to poor disease outcomes related to inflammation; however, depression is also independently and adversely associated with HIV progression via decreased CD4^{+} and CD8^{+} T lymphocytes, along with increased viral loads.[1,8]

In both disorders, the dysregulation of neuroendocrine and neuroimmunological systems (via proinflammatory cytokines) produces a cascade of events resulting in attenuation of parasympathetic tone, pain, psychomotor disturbance, depression, alterations in mood and cognition, anhedonia, fatigue, apathy, cognitive disorders, dysregulated sleep, appetite disruptions, and social withdrawal. These symptoms are collectively referred to as "sickness behavior", and are mediated by the vagus nerve (VN), along with being among the most prevalent symptoms in HIV with comorbid depression.[9–12] Chronic disruption of the VN in response to stress leads to alterations in homeostasis via constant activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathomedullary system.[13] This activation increases cytokine production, and in turn induces a chronic "sickness state". Contrarily, stimulation of the VN (particularly its α_7 nicotinic pathway) can reverse the effects of sickness behavior by producing an anti-inflammatory effect via regulation of cytokine expression.[14] In this context, HIV and depression could be pathologically related via their effect on the VN, and interventions targeting it could provide clinical benefit.

Implantable VN stimulation (iVNS) and its benefits in treatment-resistant depression have been well documented.[15–18] iVNS is achieved via a surgically implanted device; however, transcutaneous VNS (tVNS) with nonsurgical auricular technology is now available and offers potential advantages, due to its comparable benefits to VNS, ease of use, higher accessibility, and reduced side-effect profile,[19] yet the effectiveness of these technologies remains unexplored in HIV.

The main purpose of this review is to explore tVNS's potential use for depression in the HIV-infected population. First, we provide a basic overview of the VN's association to HIV and depression. Second, we briefly describe tVNS.

Third, the clinical efficacy of iVNS in depression is discussed. Fourth, studies evaluating tVNS's effectiveness in the treatment of depression since its introduction in 2010 are reviewed. Finally, implications for research and clinical practice are provided.

The vagus nerve's inflammatory association with HIV and depression

A comprehensive description of the inflammatory response is beyond the scope of this review (see Del Guerra et al[20] for a more thorough review). However, in order to understand the association between depression and HIV, a brief and basic overview of their relationship to inflammation in the context of the VN is described. Psychological stress (eg, stigmatism related to HIV diagnosis, discrimination), recurrent stressors, resilience, and the inflammatory properties of HIV are likely synergistic with the chronic activation of immune cells and resultant depression. As such, HIV and depression will be referred to as HIV-associated depression for simplicity and to indicate their relationship via immunodisruption. This section focuses on HIV as being the primary stressor that contributes to depression. Specifically, discussion is focused on sickness behavior in the context of HIV-associated depression, followed by associations with the VN.

Sickness behavior in HIV-associated depression

HIV activates T cells and monocytes (eg, CD4^{+}), which enter the CNS. Upon entry, these activated cells infect microglia and astrocytes, while also inducing the production of proinflammatory cytokines. This cell activation (together with perivascular macrophages) causes the release of neuroexcitatory amino acids (eg, glutamate), thereby disrupting calcium channels and propagating an inflammatory state. Additionally, cell activation promotes the formation and release of nonstructural proteins such as HIV-Tat and gp120. As a result, the blood–brain barrier is weakened and becomes vulnerable to peripheral cytokines, which further perpetuates the inflammatory cycle and disrupts neuronal integrity.[21,22]

As a result, locus coeruleus-norepinephrine projections to the hypothalamus and brain stem are activated. In response, the amygdala and HPA axis stimulate the release of glucocorticoids (cortisol) and activate the sympathomedullary system, which releases catecholamines (noradrenaline and adrenaline) into the peripheral blood. This activation coordinates glucocorticoid and catecholamine interaction with immune cells, thereby promoting cytokine expression and their transcription factors. Importantly, while antiretrovirals

buffer this cytokine expression, they do not completely reverse this response.[20,23]

Consequently, unsuppressed cytokine release activates an inflammatory state that manifests as "sickness or depressive behavior". Under normal conditions, this behavior is protective, and regresses as cytokines normalize along with the inflammatory response. The rebalancing of cytokines allows them to resume their trophic responsibilities in promoting neurogenesis, neuroplasticity, and maintenance of cognitive function.[24] However, in the case of HIV, this sickness behavior persists into a pathological inflammatory state. Importantly, the VN is grossly responsible for initiating sickness behavior via its interaction with cytokines, and is a critical response to immunoactivation.

Vagus nerve and sickness behavior

Herz and Kipnis[25] suggested the VN mediates sickness behavior. The VN is a major component of the autonomic nervous system, which influences neuronal, endocrine, and immune functions (neuroendocrine–immune axis) via its efferent (motor) and afferent (sensory) pathways. The vagal cholinergic anti-inflammatory pathway (CAP) interacts with the CNS, and is primarily responsible for sickness behavior.

During acute-stress states, the CAP is activated in the presence of a stressor and is responsive to proinflammatory signals that initiate an immune response. Vagal afferents detect central or peripheral pathogens (eg, via Toll-like receptors) and carry proinflammatory cytokine signals to the brain-stem nuclei. These signals are converted to the nucleus tractus solitarius and project to autonomic output centers (eg, limbic system, hippocampus, frontal cortex). The medulla coordinates this response and stimulates vagal efferent fibers, which project to the celiac ganglion.[26] Vagal fibers develop synapses on cell bodies within the celiac ganglion, thus activating innate immune responses in the spleen. Splenic nerves then release norepinephrine, which communicates with β_2-adrenergic receptor-expressing T cells. Consequently, T cells release acetylcholine to interact with α_7 nicotinic receptors, which are present on the cell surfaces of macrophages and other inflammatory cells (eg, monocytes).[27] Complex, vagal-associated brain activity and signaling inhibits inflammation due to suppression of cytokines, thereby regulating their release and stabilizing the stress response.

Contrarily, chronic inflammation (such as is the case with HIV-associated depression) interferes with the VN's ability to regulate the immune response successfully by disrupting signaling in the CAP.[28] As a result, glutamate and γ-aminobutyric acid, along with central cytokine systems, are chronically disrupted (creating a persistent proinflammatory state), which interferes with their trophic and homeostatic function. CD4+ and CD8+ T lymphocytes are dysregulated at the splenic level, which disrupts catecholamine function, thereby perpetuating stress signaling to the CNS.[1,23]

This chronic increase in cytokine and stress signaling via a disrupted CAP persistently activates the amygdala, HPA axis, and sympathomedullary system, which interferes with appetite and sleep;[11] moreover, this allows excessive cortisol to bind to glucocorticoids and increases insulin resistance. The resulting hypercortisolism and the actions of HIV's gp120 protein interferes with BDNF's energy metabolism, which supports brain health by lowering blood glucose, reducing insulin resistance, and regulating food intake.[29] Consequently, BDNF is reduced and metabolic disruptions occur, which interfere with neuroplasticity and neurogenesis.[30] Additionally, during this dysfunctional immune response, nucleus accumbens activity is significantly downregulated, which interferes with the reward pathway (motivation, pleasure, and reinforcement learning), thus promoting anhedonia and apathy.[31] Moreover, increased cytokine signaling to the basal ganglia results in psychomotor disturbances and fatigue.[32,33] The cytokine-induced CAP disruption compromises the prefrontal cortex and its functional capacity to maintain executive function, attention, memory, and adaptive social behaviors. Ultimately, this disruption perpetuates pathological social withdrawal, anhedonia, fatigue, psychomotor disturbances, and alterations to both mood and cognition or sickness behavior.[24]

The chronic-stress mechanisms in HIV-associated depression are complex and have not yet been fully elucidated; however, the overlapping symptomatology in HIV-associated depression symptoms and their relationship to VN function should be considered a potential target for treatment interventions.

Vagus-nerve stimulation

The US Food and Drug Administration approved iVNS for use in treatment-resistant depression in 2005, while tVNS was approved in Europe for depression in 2010. One such tVNS device called Nemos (developed by Cerbomed in Erlangen, Germany) has received authorization for use in epilepsy, depression, and pain conditions. Likewise, another tVNS device called GammaCore (developed by ElectroCore LLD in Basking Ridge, NJ, US) has European approval for use in prophylactic and acute treatment of migraines and headaches; however, it is not approved for depression. Currently, tVNS

is not approved in the US, but is being used for research trials across multiple populations (eg, eating disorders, rheumatoid arthritis, and irritable bowel syndrome).[34]

Transauricular vagus-nerve stimulation

The tVNS unit attaches to a battery-powered control unit that connects to a headset with bilateral electrodes, which are placed on the outer ear (see Figure 1). Alternatively, adhesive anodes and cathodes can be placed over the mastoid process juxtaposed to the outer ears. Electrodes can be applied either unilaterally or bilaterally, depending on the device specifications.[35]

Three sensory nerves supply the outer ear (ie, auriculotemporal and great auricular), but the tVNS unit specifically targets the auricular branch of the VN (ABVN) and to a lesser degree the greater auricular nerve. The ABVN predominantly innervates the external auditory meatus and concha (cymba and cavum), which provides the cutaneous access field of the ABVN targeted by tVNS.[34,36] The concha's nerve fibers provide the electrical stimulation point that allows changes in intensity, pulse duration, and frequency from the tVNS unit to induce signals via the myelinated Aβ fibers of the ABVN.[36] These ABVN fibers terminate in the nucleus of the solitary tract of the brain stem. Neuronal projections from this nucleus relay excitatory and inhibitory signals. These vagal projections are stated to be responsible for its neuroplastic, neurogenic, neuroprotective, and antidepressant properties.[37]

Stimulation can be self-administered, yet stimulation parameters have not been established; therefore, clinical models for this device do not include a standardized duration, frequency, or administration paradigm. The manufacturers recommend daily use (one to four times) for at least 1 hour (maximum of 4 hours); however, research regarding the efficacy of these specific parameters is limited. Various approaches have been researched, but are contingent on which specific tVNS unit is being utilized.[38,39] In all studies, intensity is adjusted based on perceptual tolerance and kept below each individual's pain threshold. Pain thresholds are defined as the minimal amount of stimulation that evokes a tingling or unpleasant sensation.

The side-effect profile for tVNS is appealing, due to it being the least innocuous of standard biological treatments for depression. Adverse effects tend to be stimulation-related and tend to occur during those time intervals. The most common symptoms reported are itching, outer-ear discomfort, local pain on stimulation side, and neck pain that corresponds anatomically to the location of the electrodes. Additionally, VNS can be safely used in pregnancy along with concomitant psychotropic medications (eg, antidepressants) and electroconvulsive therapy.[18]

Depression and iVNS

Approximately 21 research studies have been conducted to examine the relationship between iVNS and treatment-resistant depression. Meta-analytic and systematic reviews have found a beneficial effect for iVNS in this population.[40–42] These beneficial results support the inclusion of iVNS as a treatment option in national guidelines for depression (eg, Canadian Network for Mood and Anxiety Treatments, British
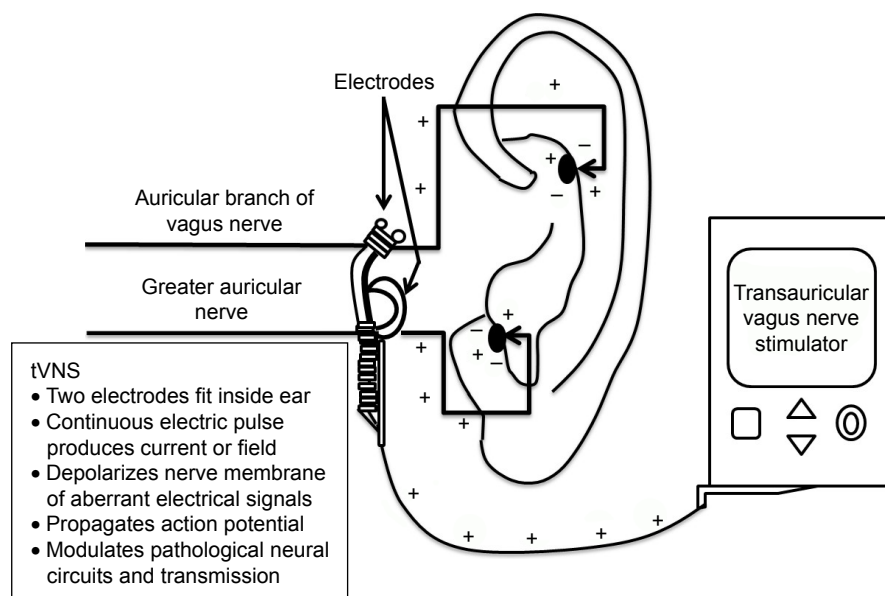
Figure 1 Transcutaneous (auricular) vagus nerve-stimulation (tVNS) device.

Association for Psychopharmacology, and National Institute for Health and Care Excellence).[41,43–45]

However, due to the methodological limitations of iVNS (cost, surgical requirements, and the higher risk posed to participants by implanting a sham device), a majority of the iVNS studies did not utilize a control group. This thus limits the inferences that can be made about the findings. Instead, most utilized a before–after design, which increases the potential for a placebo effect and could explain a portion of beneficial results, thereby minimizing the overall effect.[42]

Of note, in the studies where randomized controlled trials were utilized, results were mixed. Rush et al[46] did not demonstrate any significant benefits for VNS in a 10-week (n=235), acute, blind, randomized controlled trial. Contrarily, in a 12-month naturalistic follow-up to this study, Rush et al[47] found a significant reduction in depressive scores and global improvement. Likewise, Sackheim et al[48] conducted both a pilot and randomized controlled study. In the latter study, participants were randomized into active or sham groups (n=205), with 15% of the early responders showing a 50% reduction in depressive symptoms at 30 months and 77% maintaining this response at 24 months. Of the late responders, 20% showed a reduction at 12 months and 65% maintained this response at 24 months.

Due to the lack of adequate control trials and mixed results of the randomized studies available, more research is needed to determine the utility of iVNS as an effective intervention for treatment-resistant depression. Fortunately, the novel tVNS devices allow researchers to bypass the limitations of traditional iVNS and enable more rigorous clinical trials. As such, it is important to review the available tVNS research to determine its efficacy for depressive symptomatology and whether the advantageous nonsurgical, transauricular design improves on the previous methodological limitations of traditional iVNS. If effective, these devices could offer those experiencing HIV and comorbid depression an alternative for treatment.

Materials and methods

A systematic PubMed search of the literature was conducted on December 1, 2016 for 2010–2016. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) approach (see Figure 2) was used as the method for conducting the literature review.[49] The year 2010 was chosen due to the tVNS unit being made available to the general research market at that time. One study was conducted in 2007 that utilized this device.[50] However, it did not directly measure the effects of tVNS on depression, and

thus was not included. The search was restricted to peer-reviewed research articles published in English. Keywords operated in the search were "tVNS and depression" yielding 35 articles and "tVNS and HIV" yielding 0 articles. The tVNS and depression results were narrowed by removing the words, "epilepsy", "tinnitus", and "implantable", which resulted in ten articles. Inclusion criteria further limited the review to quantitative clinical trials and human studies, which netted five articles. Due to the small number of results, case studies were added back, resulting in a total of six articles. A more detailed review of these studies can be found in Table 1.

Results

Hein et al[38] conducted the first pilot study to explore the effects of tVNS in major depression (n=37). Two randomized sham-controlled (add-on) studies were conducted, with participants being stimulated for 5 days each week for 14 days. The first study (n=22) used an active-control group (n=11) and a sham-control group. The sham control received stimulation to the center of the left earlobe, which is without vagal innervation. Stimulation intensity was 0–600 mA with a frequency of 1.5 Hz for 15 minutes daily. Ranges were adjusted just below the participant's perception threshold. In the second study (n=15), seven participants were given active stimulation while the remaining received sham stimulation. However, the stimulation occurred for 15 minutes twice daily (morning and evening) with fixed parameters of 130 mA and 1.5 Hz. The Hamilton Depression Rating Scale (HAM-D) and Beck Depression Inventory (BDI) were administered at baseline (day 0) and at the conclusion of the study (day 14). Using pooled analysis, both studies showed a significant mean difference between the active and sham groups on the BDI. Contrarily, neither showed significant differences on the HAM-D. No significant side effects were noted due to tVNS use.

Trevizol et al[35] reported the first case-study utilizing tVNS in a 38-year-old man with major depression. This patient received stimulation for 5 days each week for 14 days at 120 Hz with a pulse duration of 250 µs for 30 minutes daily. The HAM-D was administered at baseline along with the Montreal Cognitive Assessment. After 14 days, this patient's symptoms went into complete remission and remained stable at a 2-month follow-up. No significant side effects were noted due to tVNS use.

Trevizol et al[51] conducted a proof-of-concept trial (n=12) exploring the effects of tVNS in major depressive disorder. The HAM-D was the primary instrument used to evaluate depression, with end-point response defined as a 50%
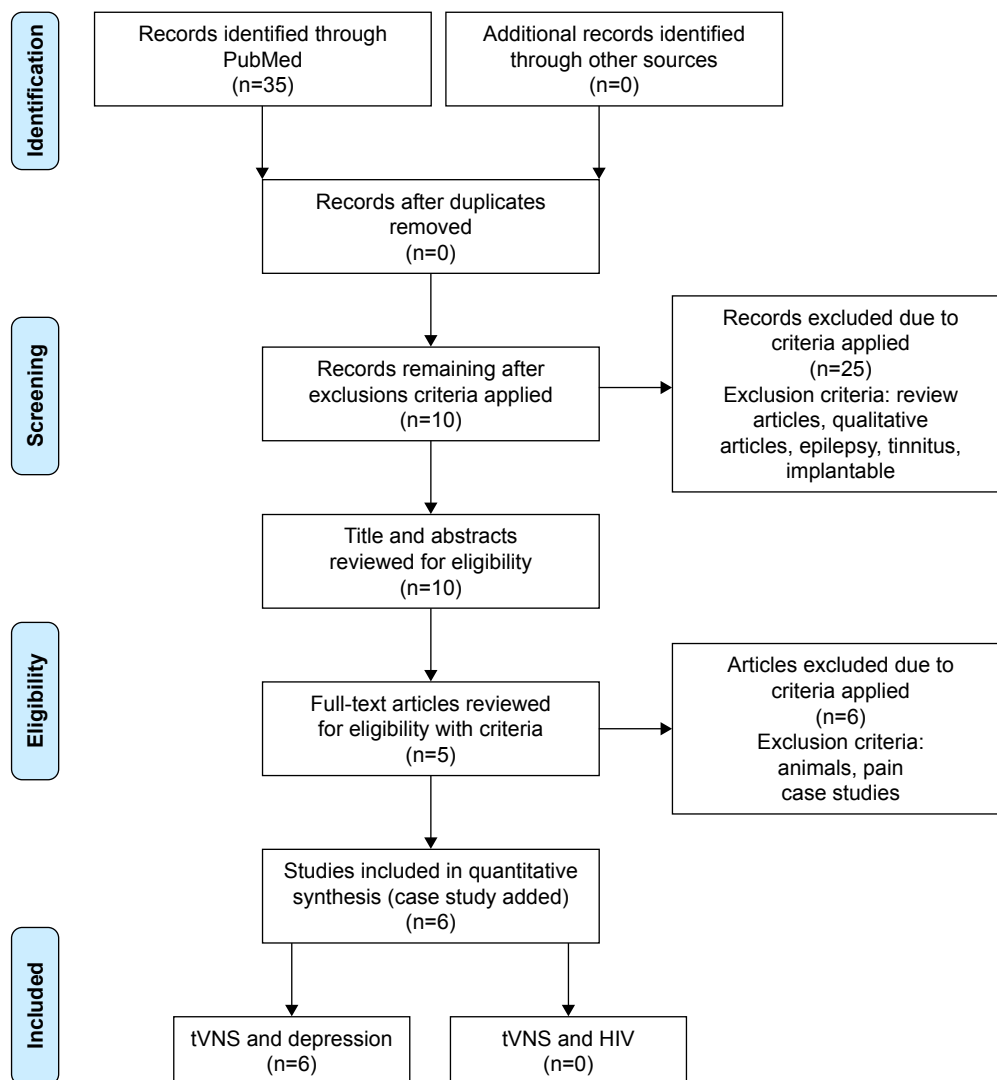
Figure 2 PRISMA flow diagram demonstrating screening method for articles.
Note: Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.[49]
Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; tVNS, transcutaneous vagus nerve-stimulation.

reduction in baseline scores. Patients received stimulation for 5 days each week for 14 days at 120 Hz with pulse duration of 250 µs, and intensity was set at 12 mA for 30 minutes daily. After 14 days, all participants demonstrated a clinical response with a 50% reduction in depressive symptoms. Five patients exhibited remission of depressive symptoms (score of <8 on the HAM-D). Response was maintained at 1-month follow-up. Cognition remained stable, as measured by the Montreal Cognitive Assessment. No adverse effects were reported. Ten participants reported diurnal sleepiness after stimulation, with six patients experiencing nausea, but no medication or treatment was required. There were no dropouts reported.

Fang et al[52] conducted a single-blinded clinical trial (n=49) exploring the effects of tVNS in mild–moderate

major depression. A total of 34 patients were included in the study analysis (after 14 dropped out and one was excluded for excessive head movement), and were divided into active (n=18) and sham (n=16) groups. The active group received stimulation at 20 Hz with a wave width less than 1 ms with intensity adjusted based on tolerance or perception threshold (4–6 mA). Stimulation occurred twice a day for 30 minutes at least 5 days a week for 1 month. After functional magnetic resonance imaging (fMRI) and HAM-D to evaluate depression symptoms, the results supported the efficacy of tVNS, as significant decreases in depressive symptoms (≤50% reduction) were found. In support, the fMRI results corresponded to increased functional connectivity in the default-mode network of the brain (known to be decreased in depression). No significant side effects were noted due to tVNS use.

Table 1 Summary of transcutaneous vagus nerve stimulation treatment studies of major depression

Study	Participants	VNS parameters	Procedure and measures	Data analysis/findings	Strengths and limitations
Hein et al[38]	Study 1 n=22 (mean age 44 years; male/female 9/13) Two randomized groups: tVNS (n=11), sham (n=11) Study 2 n=15 (mean age 48 years; male/female 6/9) Two randomized groups: tVNS (n=8), sham (n=7)	Study 1 Intensity: 0–600 mA; not fixed Frequency (Hz): 0.5–100 15 minutes daily/14 days Study 2 Intensity: 130 mA; fixed Frequency (Hz): 1.5 15 minutes/2× daily/14 days	Study 1 Bilateral NET-2000 TENS unit inserted, inner ear Sham: same procedure; no stimulation Study 2 Bilateral NET-1000 tVNS unit inserted, inner ear Sham: same as above Outcome measures Reduced scores on BDI and HAM-D	Study 1 BDI scores reduced from 27 to 14 in active group No reduction in sham Study 2 BDI scores reduced from 31 to 25.8 in active group No reduction in sham Overall No changes in HAM-D in either study	Strengths Naturalistic Limitations Short duration Cotreatment with antidepressants/psychotherapy No blinding Small study
Trevizol et al[35]	n=1 (38-year-old man), case study	Stimulation: 120 Hz, 250 µs 30 minutes daily/14 days	tVNS external device used Autoadhesive rubber electrodes of 20 cm² placed over the mastoid process bilaterally Outcome measures Reduced scores on HAM-D	HAM-D scores improved Remission achieved (<8)	Strengths Novel study Limitations Case study No sham or control
Trevizol et al[51]	n=12 (mean age 45.9 years; male/female 2/10) No randomized groups	Intensity: 12 mA Stimulation: 120 Hz, 250 µs duration 30 minutes daily/14 days	Neurodyn II external device used Autoadhesive rubber electrodes of 15 cm² placed over the mastoid process bilaterally Outcome measures 50% or greater reduction of scores on HAM-D	HAM-D reduction from 27.9 to 8.2 (mean difference 19.75, SD 4.2) All exhibited ≥50% reduction in scores Five participants exhibited remission (<8) Response maintained at 1 month follow-up	Strengths Proof of concept Follow-up Limitations No sham, blinding, or randomization Convenience sample
Fang et al[52]	n=34 (mean age not reported; male/female not reported) Two randomized groups: tVNS (n=18), sham (n=16)	Intensity: 4–6 mA Stimulation: 20 Hz of 1 ms duration 30 minutes 2× daily/4 weeks	40-minute device training Seated position or laying on side with electrode clips attached bilaterally Self-administration at home; complete daily log; log checked every 4 weeks Sham treatment self-administered; electrodes clipped to superior scapha with no vagal connection; required to complete daily entries in a diary log for 4 weeks Outcome measures Primarily reduced scores on HAM-D (>50%) Secondarily reduced scores on HAM-A, SAS, and SDS	Depression scores reduced on HAM-D in tVNS group Significant interaction between treatment and sham group and treatment time on all measures (except HAM-A)	Strengths Randomized Single-blind Longer duration Sham stimulation Limitations Self-administered Self-administered sham protocol Self-record logs Small study

(Continued)

Table 1 (*Continued*)

Study	Participants	VNS parameters	Procedure and measures	Data analysis/findings	Strengths and limitations
Rong et al[39]	n=160 Two randomized groups: tVNS (n=91, mean age 40.1 years; male/female 23/68), sham (n=69, mean age 43.88 years; male/female 20/49)	Intensity: 4–6 mA Stimulation: 20 Hz of 0.2 ms 30 minutes 2× daily/12 weeks	Same protocol as Fang et al,[52] with exception of an active control After 4 weeks, sham group received tVNS for 8 weeks <u>Outcome measures</u> Primarily reduced scores on HAM-D (>50%) Secondarily reduced scores on HAM-A, SAS, and SDS	<u>Week 4 (0–4)</u> HAM-D scores reduced in both groups; significantly greater in tVNS group Significant changes between treatment and sham group on HAM-D No significant response between tVNS group (at 4 weeks or 4–8 weeks) and sham (at 4–8 weeks or 8–12 weeks) <u>Week 12</u> Significant response between tVNS groups at 0–4, 4–8, and 8–12 weeks	<u>Strengths</u> Randomized Naturalistic Active control Large study Longer duration Sham stimulation <u>Limitations</u> Self-administered sham protocol Self-record logs
Liu et al[53]	n=49 Two randomized groups: tVNS (n=18, mean age 37.83 years; male/female 6/12), sham (n=16, mean age 42.56 years; male/female 5/11)	Intensity: 4–6 mA Stimulation: 20 Hz of <1 ms 30 minutes 2× daily/4 weeks	Same protocol as Fang et al[52] <u>Outcome measures</u> Primarily reduced scores on HAM-D (>50%) Secondarily reduced scores on HAM-A, SAS, and SDS	HAM-D scores reduced Significant interaction between treatment and sham groups and treatment time on all measures Significant interaction on HAM-D subscales between tVNS and sham group	<u>Strengths</u> Randomized Single-blind Large study Longer duration Sham stimulation <u>Limitations</u> Self-administered Sham protocol Self-record logs

Abbreviations: BDI, Beck Depression Inventory; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; NET, neuroelectric therapy; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; TENS, transcutaneous electrical nerve stimulation; tVNS, transcutaneous (auricular) vagus nerve stimulation.

Rong et al[39] conducted a nonrandomized study (n=160). The study was divided into an active group (n=91) that received tVNS for 12 weeks and a control group (n=69) that received sham stimulation for 8 weeks followed by 4 weeks of tVNS. A total of 148 participants completed the trial at 1 month and 138 participants at 2 months. Stimulation parameters were set at 20 Hz (width of 0.2 ms), with intensity increased gradually from 0 until tolerance threshold was achieved (4–6 mA). As per the other studies' protocols, stimulation was administered twice daily for 30 minutes per session. Depression was assessed using the HAM-D. After 1 month of treatment, there was a significant difference between the active group and the sham group with a decrease in scores (≤50% reduction). Additionally, this improvement was maintained at 12 weeks. Interestingly, this study explored subgroups within the tVNS participants to determine if there was a difference in response when comparing mild (HAM-D score of <20) to moderate depression. Although the effect size was smaller, this study demonstrated a significant reduction in mild symptoms as well. No adverse side effects were noted due to tVNS use.

Utilizing the same experimental and stimulation procedures same as Rong et al[39] and Lui et al,[53] research from Fang et al[52] conducted a single-blind clinical trial (n=49) exploring the neurological effects of tVNS in depression. Stimulation occurred over a 1-month period. Resting fMRI scans were conducted pre- and post-tVNS intervention, while depressive symptomatology was assessed utilizing the HAM-D as the primary end point. After 1 month of treatment, HAM-D scores significantly reduced in the tVNS group when compared to the sham. Moreover, the functional connectivity between the amygdala–lateral prefrontal networks showed a significant increase. Increases in this resting-state connectivity corresponded to the HAM-D reduction in depressive symptomatology. No significant side effects were noted due to tVNS use.

Discussion

The purpose of this review was to examine tVNS's potential use in HIV-associated depression via a review of its use in the depression population. Overall, the results of the review are promising and support the findings of previous studies that utilized traditional iVNS devices. Each found a significant reduction in depressive symptoms. Furthermore, as expected, no significant side effects occurred from utilizing the tVNS units. In an effort to standardize stimulation parameters, each study relied on a similar protocol developed by Hein et al[38] for experimental reference and utilized similar procedures.

This effort and replication of positive results provides the first step in developing a standardized clinical paradigm for the use of tVNS in a clinical setting for depression. Contrarily, the limited stimulation parameters (see parameters in Table 1) restrict interpretability or feasibility of use outside those parameters. In reference to HIV-associated depression, its utilization could require a different stimulation protocol that has not yet been researched.

Interpretations of positive results should be approached with caution, as there were few research studies available, which restricts any conclusive statements about tVNS's efficacy. While some were adequately powered,[39] other trials were restricted to a case-study design[35] or used participants from the same cohort.[52,53] Additionally, due to one instrument being utilized as the outcome measure (HAM-D) in each of these studies, it cannot be ruled out that this instrument is not capturing a heterogeneous population.

Simply, contention surrounds the accuracy of HAM-D cutoff scores for remission versus active depression. In addition, it does not include specific diagnostic information, which is included in other depression-screening scales, thereby providing a more general assessment of depression. Therefore, the construct validity of the HAM-D is of concern, due to it lacking the conceptual clarity of other available measures. This limitation could restrict the HAM-D's identification of depressive symptom subtypes.[54] For example, Hein et al[38] found depressive symptoms remitted utilizing the HAM-D in both the sham and control groups. A similar effect was found in Fang et al.[52] This finding could suggest that the improvements in depression as it relates to tVNS are not as specific in the HAM-D versus other scales; therefore, this could affect interpretability in the context of various types of depression (such as HIV-associated depression). Despite these methodological limitations, the results of this review suggest tVNS should be considered as a treatment option for HIV-associated depression.

Limitations to this review were the restriction of review articles to those in English. It is possible that other research trials have been published in the non-English literature, which could have added valuable results to this review. Considering the lack of research examining tVNS and depression in humans, animal studies (which have to be considered with caution) could have provided a deeper understanding of tVNS's potential use in HIV-associated depression.

Implications for HIV research

Based on this review, the most compelling evidence for tVNS's use in HIV-associated depression was found in the

studies conducted by both Fang et al[52] and Lui et al.[53] Each of these studies explored the neurological effects of tVNS on depression via brain imaging and rating scales. The results identified improved functional connectivity in the default-mode network (eg, hippocampus, amygdala, medial prefrontal cortex, and anterior cingulate), which is involved in affect, cognition (particularly prospective memory), and emotional regulation. This confirms previous studies in depression that have implicated altered default-mode network connectivity as playing a primary role in its expression. Moreover, studies have shown cytokines have a profound effect on this network, and its sensitivity to inflammation has been linked to depression and cognitive impairment.[55]

Evidence from the HIV CHARTER cohort study suggests depressive episodes (over a lifetime) were present in approximately 50% of cases with neurocognitive impairment.[56] Interestingly, in a cross-sectional study (n=111, 58 HIV⁺ and 53 HIV⁻), Thomas et al[57] demonstrated diminished functional connectivity in the default-mode network as playing a critical role in the neurodegenerative process of HIV or more specifically HIV-associated neurocognitive disorder (HAND). Furthermore, they demonstrated HIV's disruption of connectivity in the salience and executive-control networks that are responsible for working memory and emotional conflict processing.

In a recent short-term study with 30 healthy adults (15 women), Jacobs et al[58] found tVNS improved associative-memory performance when compared to a control group. These researchers' hypothesized that tVNS mediated stress-related effects (eg, inflammation) on memory function via its interaction with β-adrenergic receptors located on afferent vagal fibers that project into the nucleus tractus solitarius. This vagal activation stimulates the locus coeruleus to release norepinephrine, thereby modulating cortical and subcortical network activity. The results suggest tVNS changes the functional pathways for learning and consolidation that favor neuroplasticity. Interestingly, functional decline in learning efficiency and memory retrieval has increased in HIV during the antiretroviral era.[59]

Bachis et al[29] demonstrated BDNF's ability to inhibit HIV's gp120 protein, showing an inverse relationship in its expression. This suggests BDNF helps reduce microglial and astrocyte infection in the CNS via independent and anti-inflammatory properties. Therefore, they posited that increased BDNF could counteract gp120's interaction with monocytes. Interestingly, Biggio et al[60] demonstrated long-term iVNS's ability to increase BDNF expression in the hippocampus and induce neuroplasticity. This effect diminished after 3 weeks without iVNS. They concluded that long-term BDNF promoted the survival and trophism of new granule cells in the hippocampus, which persisted in the presence of iVNS.

In support of this, Furmaga et al[61] demonstrated iVNS promoted increased BDNF activity via phosphorylation of its primary receptor (TrkB). These researchers noted that this activity provided an antidepressant effect that was independent of those accomplished with antidepressant medications. This mechanism suggests tVNS could augment current antidepressant medications (eg, paroxetine, sertraline), thus providing an enhanced effect or offering an alternative neurological pathway for treatment. Importantly, tVNS has been shown to modify proinflammatory cytokines in murine models.[62] More recently, in a healthy sample of 20 men and women, Lerman et al[63] demonstrated tVNS's ability to downregulate inflammatory cytokines in the context of lipopolysaccharides (induce an inflammatory response). While tVNS has not been explored in the context of BDNF, research supports its comparability to iVNS. This suggests that tVNS could help provide both anti-inflammatory and antidepressant effects for HIV-associated depression via increased BDNF activity and cytokine regulation. Additionally, tVNS could possibly provide a treatment option for HAND.

Not only are the results promising in these pilot studies as relates to depression, but other tVNS studies have implications in conditions that comorbidly present in HIV and depression alike. For example, Ay et al[64] demonstrated in rat models that cutaneous VNS inhibited cerebral ischemia-induced immunoactivation. Furthermore, it reduced the degree of tissue injury and functional deficiencies that resulted from the cerebral event. The effectiveness in ischemia has implications for HIV and related cerebrovascular pathology. HIV patients are admitted to hospitals 60% more often for stroke, despite a reduction in overall hospitalizations in the general population. Research suggests cerebrovascular inflammation via chronic immunoactivation could play a critical role in HAND.[21] Likewise, Ayerbe et al[65] reported a 29% prevalence of depression up to 10 years poststroke, with a 40%–52% cumulative incidence within 5 years. Importantly, predictors of this depression were prestroke depression and cognitive impairment.

Currently, no studies exist that explore tVNS as a treatment option for HIV; furthermore, no infectious models exist in nonhumans that can actually duplicate the physiological effects HIV has on humans, which suggests the need to test it directly in adults with HIV.[66] The safety, effectiveness,

and tolerability of tVNS have been reviewed for sepsis, atrial fibrillation, depression, epilepsy, migraines, and tinnitus, which provides a strong foundation for its use in HIV. In consideration of current knowledge and available technology, research in HIV-associated depression is warranted with tVNS. The potential benefits of this research are not restricted to depression or cognitive disorders, but could also be utilized as a buffer to comorbidities associated with HIV (eg, stroke, metabolic disruptions, and neuropathy) or that result as a consequence of HIV treatment.

Implications for clinicians

The safety, efficacy, and self-administration capabilities of the tVNS units have clinical utility for clinicians. If research determines their efficacy in the HIV population, these devices could provide a cost-effective and safe alternative for HIV-associated depression treatment. In an outpatient setting, these devices can be calibrated, prescribed for use at home, and utilized as augmenting agents to standard antidepressant treatments or individual therapies for comorbid depression and HIV symptomatology (eg, cognitive disorders). If effective, these devices could help reduce the polypharmacy often faced in HIV by replacing select psychotropic medications and select cardiovascular medications;[67] moreover, they could potentially alleviate or help control common side effects that result from the use of these medications (eg, QRS elongation, tinnitus, headaches, metabolic disturbances, and motor dysfunction).[68–70]

Disclosure

The authors report no conflicts of interest in this work.

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