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Review Article

Non-invasive Vagus Nerve Stimulation for the Treatment of Neurological & Psychiatric Disorders: A Narrative Review

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Abstract

Non-invasive vagus nerve stimulation (nVNS), including transcutaneous cervical (tcVNS) and auricular (taVNS) modalities, has garnered increasing attention as a neuromodulatory therapy for various neurological and psychiatric disorders. This narrative review synthesizes findings from over 80 studies, including randomized controlled trials, meta-analyses, and observational research published up to March 2024, evaluating nVNS in epilepsy, depression, stroke rehabilitation, headache, Parkinson's disease, and Alzheimer's disease. Evidence suggests that taVNS can reduce seizure frequency and improve quality of life in epilepsy. In major depressive disorder, nVNS demonstrates antidepressant effects comparable to pharmacotherapy, though the optimal stimulation parameters remain unclear. For post-stroke motor rehabilitation, both tcVNS and closed-loop stimulation systems enhance neuroplasticity and motor recovery. In Parkinson's and Alzheimer's diseases, preliminary findings indicate possible modulation of neuroinflammatory pathways and cognitive-motor functions, although recent meta-analyses report mixed efficacy. Challenges include methodological heterogeneity, protocol variability, and difficulties in designing effective sham controls, all of which limit the generalizability of current findings. Mechanistic differences between tcVNS and taVNS remain inadequately characterized. Overall, nVNS appears to be a safe and accessible therapeutic approach with broad clinical potential, particularly for treatment-resistant or underserved populations. However, future research must prioritize standardized protocols, robust clinical endpoints, and adequately powered trials to define efficacy and optimize treatment strategies. A greater focus on long-term outcomes, biomarker-guided personalization, and clinical significance over statistical findings will be critical in translating nVNS into routine practice.

Introduction

Vagus nerve stimulation (VNS) is a well-established neuromodulation technique with a long history of therapeutic applications. The first documented experiments on VNS date back to the late 1800s, conducted by Dr. James Corning. Over the past century, both invasive and noninvasive VNS have shown significant potential in treating a range of neurological and psychiatric disorders. Initially developed for drug-resistant epilepsy, VNS has since been approved for treatment-resistant depression and explored for post-stroke motor rehabilitation.[1] Beyond these established indications, research continues to investigate its role in managing conditions such as Alzheimer's disease (AD),[2] Parkinson's disease (PD),[3] traumatic brain injury,[4,5] tinnitus,[6] chronic pain, and sleep disorders.[7]

Traditionally, VNS was administered via a surgically implanted device, with electrodes wrapped around the cervical vagus nerve and connected to a pulse generator implanted in the chest. While effective, this approach carries surgical risks—including infection, vocal cord paralysis, and device-related complications—limiting its broader applicability, especially in patients with comorbidities.

To overcome these limitations, noninvasive vagus nerve stimulation (nVNS) has emerged as a safer, more accessible alternative. Two primary forms of nVNS are transcutaneous cervical VNS (tcVNS), which targets the vagus nerve at the neck, and transcutaneous auricular VNS (taVNS), which stimulates the auricular branch of the vagus nerve in the ear. These modalities have gained attention due to their favorable safety profile, patient tolerability, and ease of self-administration. The U.S. Food and Drug Administration (hereinafter referred to as FDA) has approved nVNS de-

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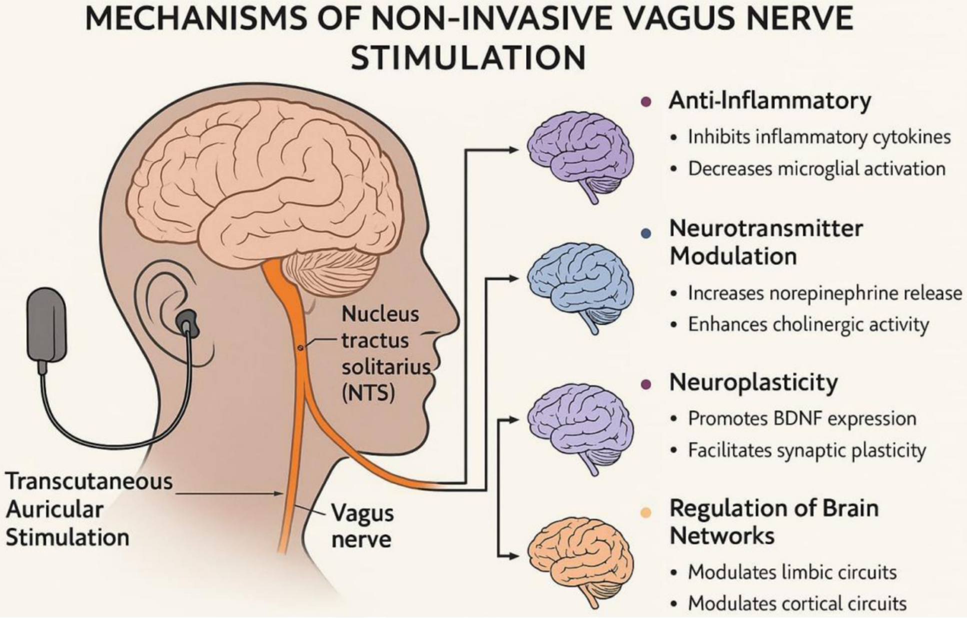

Fig. 1. Major mechanisms of non-invasive vagus nerve stimulation (nVNS).

vices for the acute and preventive treatment of cluster headaches and migraines, reinforcing their growing clinical relevance.[8]

Recent systematic reviews and meta-analyses suggest that taVNS and tcVNS may offer therapeutic benefits across various conditions. These include reducing seizure frequency in epilepsy,[9] alleviating depressive symptoms,[10] relieving tinnitus,[11] and enhancing motor recovery after stroke when paired with rehabilitation.[12] Importantly, recent meta-analyses have reported mixed or marginal efficacy in disorders such as PD, emphasizing the need for further high-quality trials. Additionally, emerging evidence suggests the potential application of nVNS for neuropsychiatric complications of Long COVID,[13] indicating a broader therapeutic role.

With the evolution of personalized medicine, innovations such as closed-loop stimulation systems—tailoring electrical output in response to real-time physiological feedback—are under active investigation. Despite its promise, challenges remain. These include variability in stimulation parameters across studies, lack of unified protocols, and difficulties in standardizing sham conditions for clinical trials—factors that complicate the interpretation and comparison of findings.

This review aimed to provide a comprehensive overview of the mechanisms, clinical applications, and current evidence base for nVNS, critically appraising studies across major neurological and psychiatric disorders. It also outlines future directions in the field, including the optimization of stimulation parameters, exploration of novel indications, and the development of standardized guidelines to support clinical translation.

nVNS

nVNS exerts its therapeutic effects through modulation of both peripheral and central pathways. Stimulation of vagal afferent fibers—via auricular (taVNS) or cervical (tcVNS) branches—sends signals to the nucleus tractus solitarius in the brainstem, which then projects to key regions such as the limbic system, cortex, and autonomic control centers. This cascade enhances the release of neurotransmitters, including noradrenaline, serotonin, and acetylcholine, which regulate mood, cognition, and pain perception.[14] Activation of the locus coeruleus further amplifies noradrenergic tone, contributing to arousal, attention, and neuroprotection.[15]

nVNS also modulates immune responses by suppressing microglial activation, reducing pro-inflammatory cytokines (e.g., interleukin-1beta (IL-1β), tumor necrosis factor-alpha), and inhibiting the P2X7R/NLRP3 inflammasome pathway. These actions help mitigate neuroinflammation, a key factor in various central nervous system pathologies. Additionally, nVNS enhances neuroplasticity and neuronal resilience by upregulating brain-derived neurotrophic factor, which supports synaptic integrity and recovery from injury.[16]

Through this multifaceted influence on neural, chemical, and immune pathways, nVNS holds potential as a neuromodulatory tool for improving brain function and restoring physiological balance in dysregulated systems (Fig. 1).

nVNS for neurological diseases

Epilepsy

Epilepsy is one of the most prevalent neurological disorders worldwide, affecting approximately 50 million people.[17] Each year, five million individuals are newly diagnosed, and despite advancements in pharmacotherapy, 20–40% of these patients develop drug-resistant epilepsy (DRE).[17] Psychiatric comorbidities, including anxiety and depression, are also highly prevalent in this population, underscoring the need for alternative, non-pharmacological treatment strategies.

Recent research has focused on nVNS, particularly taVNS and tcVNS, as emerging modalities in epilepsy management. Early pilot studies have demonstrated the feasibility, safety, and tolerability of taVNS, paving the way for larger randomized controlled trials (RCTs) to evaluate its efficacy in patients with DRE.[18,19]

One of the first RCTs, conducted by Liu *et al*.,[20] involved a

12-month trial in pediatric and adult patients with medication-resistant epilepsy. The results showed a significant reduction in monthly seizure frequency in the active taVNS group compared to controls. Furthermore, all 60 participants reported improvements in anxiety, depression, and quality of life, with only minimal and transient adverse effects.

In a 2014 multicenter RCT, Rong *et al*.[21] evaluated taVNS in 50 patients aged 12 and older with DRE. Among the 47 participants who completed the trial, 12% achieved seizure freedom after eight weeks, and 24% experienced a reduction in seizure frequency. These numbers increased by 24 weeks, with 16% seizure-free and 38% showing reduced seizure frequency.

Building on this, Rong *et al*.[22] later conducted a larger multicenter RCT involving 144 patients with pharmacoresistant epilepsy. After eight weeks of blinded stimulation, seizure reduction was observed in 41% of the active taVNS group compared to 27.5% in controls. By 24 weeks, seizure reduction was comparable between the active group (47.7%) and those who crossed over from sham (47.5%), suggesting sustained benefits with prolonged stimulation.

The only double-blind multicenter RCT to date, conducted by Bauer *et al*.[23] in 2016, randomized 76 patients to receive either 1 Hz or 25 Hz taVNS. After 20 weeks, responder rates were 25% and 50%, respectively, with high adherence across both groups. A significant reduction in seizure frequency was observed in the 25 Hz group, suggesting a dose-dependent effect.

Additional studies by Barbella, Liu, and others have further supported the therapeutic potential of taVNS, although findings remain heterogeneous.[24,25] A recent RCT by Yang *et al*.[26] randomized 150 patients to receive 20 weeks of either active or sham taVNS. The active group demonstrated a greater reduction in seizure frequency, but no significant differences were found in secondary outcomes related to mood, cognition, or quality of life, highlighting areas for further investigation.

Overall, as summarized in Table 1, taVNS has demonstrated consistent safety and acceptability across studies, with few adverse events reported.[20–23,26–44] While the accumulated evidence supports its role as a promising adjunctive therapy for drug-resistant epilepsy, variability in stimulation protocols, sham conditions, and outcome measures presents ongoing challenges. Future research should prioritize large-scale, multicenter trials with standardized methodologies to refine stimulation parameters and better assess long-term efficacy in diverse patient populations.

Depression

Major depression is a widespread and debilitating condition, consistently ranked among the leading causes of disability globally. Its prevalence has steadily increased over the past two decades, with annual rates of major depressive episodes reaching up to 7.1%.[45] The burden of major depressive disorder (MDD) and treatment-resistant depression (TRD) extends beyond individual suffering, affecting families, workplaces, and healthcare systems. Given high relapse rates, limited access to care, and suboptimal treatment responses, there is growing interest in innovative, accessible therapeutic alternatives.

taVNS, a non-invasive neuromodulatory technique, has emerged as a promising adjunctive or stand-alone treatment for depression. Compared to invasive VNS, taVNS offers advantages such as increased accessibility, cost-effectiveness, and the potential for home-based, self-administered therapy. Its non-invasive nature also facilitates mechanistic studies, accelerating clinical translation.

A recent study published in reported that 40% of patients achieved a 50% reduction in depression severity on the Montgomery–Åsberg Depression Rating Scale (MADRS) and ≥50% reduction on the Hamilton Depression Rating Scale (DRS).[46] Several exploratory trials have investigated the antidepressant potential of taVNS, though findings remain mixed due to methodological differences.

Hein *et al*.[27] conducted the first double-blind, RCT of taVNS in MDD, enrolling 37 participants for two weeks of active or sham stimulation. The active group showed significant improvement on the Beck Depression Inventory, although no between-group differences emerged on the Hamilton Depression Rating Scale (HAM-D), highlighting variability in outcome measures.

Rong *et al*.[28] later conducted a non-randomized controlled pilot trial over 12 weeks, where the active group received continuous stimulation, while controls underwent four weeks of sham stimulation before switching. Greater improvements on the HAM-D were observed in the active group, with sustained benefits through week 12.

In an open-label study, Trevizol *et al*.[29] found significant reductions in HAM-D scores after 10 taVNS sessions over two weeks, with effects maintained at a 45-day follow-up. Another study showed improvement in treatment resistant depression with long term use of VNS.[47] However, replication in larger, blinded studies is needed to confirm efficacy and minimize placebo effects. Preliminary studies have also explored taVNS in pediatric populations and post-stroke depression,[48,49] although evidence remains early.

Overall, as summarized in Table 1, taVNS is a safe and well-tolerated intervention with modest antidepressant effects. Future large-scale RCTs with standardized protocols are essential to determine efficacy, optimize dosing, and assess long-term outcomes. Biomarker research and individualized strategies may further refine its role in treating MDD and TRD.

Post-stroke rehabilitation

VNS for post-stroke motor rehabilitation represents a promising application of neuromodulation, building on preclinical models and advancing into human clinical studies. Stroke remains the second leading cause of death and long-term disability globally, with its prevalence expected to rise significantly by 2030.[50] Despite advances in acute stroke care, many survivors are left with persistent motor deficits that severely impact their independence and quality of life. Although conventional rehabilitation can harness neuroplasticity, many patients experience limited recovery, even with intensive therapy. These challenges highlight the need for adjunctive strategies to enhance motor rehabilitation.

nVNS has emerged as a potentially accessible and scalable intervention for improving post-stroke motor outcomes. Among nVNS modalities, taVNS has been most frequently studied, though with variability in stimulation parameters, electrode placement, and patient selection.[30–33] Notably, three out of four published studies targeted the left cymba concha, while one used the left acoustic meatus. As summarized in Table 1, one small open-label trial found that 87% of participants (n = 13) showed clinically meaningful gains in upper limb function, as measured by the Fugl-Meyer Assessment for Upper Extremity.[31] Additionally, three small RCTs demonstrated that stroke survivors receiving active taVNS alongside physical therapy achieved significantly greater motor improvements than those receiving sham stimulation.[30,32,33] These findings align with results from invasive cervical VNS studies, which demonstrated two- to three-fold improvements in motor outcomes when stimulation was paired with therapy. A systematic review by Xiao *et al*.[34] confirmed that taVNS combined with rehabilitation significantly outperformed rehabilitation alone in upper

Table 1. Depicting the major studies involving nVNS and their key findings

Condition	Study	Design	Sample size	Key findings
Epilepsy	Liu *et al.*[20]	RCT	60	Significant seizure reduction, improved mood/QoL, minimal adverse effects
Epilepsy	Rong *et al.*[21] (2014)	Multicenter RCT	50	16% seizure-free, 38% reduced frequency at 24 weeks
Epilepsy	Rong *et al.*[22] (later study)	Multicenter RCT	144	47.7% seizure reduction at 24 weeks in active group
Epilepsy	Bauer *et al.*[23] (2016)	Double-blind multicenter RCT	76	Dose-dependent effect; 25 Hz group had 50% responders
Epilepsy	Yang *et al.*[26] (2023)	RCT	150	Greater seizure reduction in active group; no difference in mood/cognition/QoL
Depression	Hein *et al.*[27]	Double-blind RCT	37	BDI improved; no significant HAM-D difference
Depression	Rong *et al.*[28]	Non-randomized controlled pilot	49	Greater HAM-D improvement in active taVNS group.
Depression	Trevizol *et al.*[29]	Open-label	12	Reduced HAM-D scores, sustained at 45-day follow-up
Post-stroke rehab	Capone *et al.*[30]	Randomized pilot study	20	Combined taVNS significantly improved motor scores compared to rehab alone
Post-stroke rehab	Redgrave *et al.*[31]	Open-label pilot study	14	Clinically meaningful improvements in upper limb function after taVNS plus rehab
Post-stroke rehab	Baig *et al.*[32]	Open-label exploratory study	10	Improvement in somatosensory function; sustained post-intervention with taVNS plus task-specific training
Post-stroke rehab	Wu *et al.*[33]	Randomized controlled pilot trial	60	Significant improvement in motor function in taVNS group
Post-stroke rehab	Xiao *et al.*[34] (2021)	Systematic review	Nine studies	taVNS + rehab superior to rehab alone in upper limb function
Headache	PRESTO trial[35]	Large RCT	248	tcVNS is effective for acute migraine relief at 30–60 m
Headache	Silberstein *et al.*[36] (ACT1)	RCT	133	34.2% relief at 15 m in cluster headache (vs. 10.6% sham)
Headache	Goadsby *et al.*[37] (ACT2)	RCT	92	Significantly higher pain-free rates in nVNS vs sham at 15 m ($p = 0.02$) for episodic cluster headaches
Headache	Simmonds *et al.*[38] (PREVA study)	RCT	248	tcVNS reduced the attack frequency in chronic cluster headaches
Headache	PREMIUM trial[39]	Largest RCT for migraine prevention	332	No significant difference in frequency; some subgroup benefits
Parkinson's disease	Farrand *et al.*[40] (2020)	Experimental study	18	Different VNS paradigms had differential effects on motor and non-motor symptoms, higher-frequency VNS led to improved motor function and mood, and lower-frequency VNS may be better for safety and cognitive function
Parkinson's disease	Eissazade *et al.*[41] (2020)	Pilot study	10	Significant improvements in motor function and cognitive symptoms, particularly in attention and executive function
Parkinson's disease	Abouelmagd *et al.*[42] (2023)	Meta-analysis	8 RCTS	Non-invasive VNS significantly improved motor function and quality of life but had mixed effects on cognitive symptoms
Parkinson's disease	Song *et al.*[43] (2024)	Systematic review and meta-analysis	12 RCTS	Significant improvement in motor function (UPDRS) and some non-motor symptoms (depression, cognition)
Alzheimer's disease	Wang *et al.*[44]	RCT	80	taVNS significantly improved cognitive function in MCI patients compared to sham treatment, with a good safety profile

ACT, acute treatment of cluster headache; BDI, Beck Depression Inventory Scale; HAM-D, Hamilton Depression Rating Scale; MCI, mild cognitive impairment; nVNS, non-invasive vagus nerve stimulation; PREMIUM, Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management; PRESTO, PRospectivE Study of nVNS for the acute Treatment of migraine; PREVA, PREVention and Acute treatment of chronic cluster headache; QoL, quality of life; RCT, randomized controlled trial; taVNS, transauricular vagus nerve stimulation; tcVNS, transcervical vagus nerve stimulation; UPDRS, Unified Parkinson' Disease Rating Scale; VNS, vagus nerve stimulation.

limb recovery.

However, the current evidence is limited by small sample sizes, short follow-up durations, and methodological heterogeneity. Differences in stimulation parameters and timing further complicate the identification of optimal protocols. Large, multicenter RCTs are crucial to validate early findings and establish standardized guidelines.

Recent innovations have introduced motor-activated auricular VNS, a closed-loop system that delivers stimulation in response to voluntary movement detected via surface electromyography.[51] This technique synchronizes stimulation with motor intent, potentially enhancing neuroplasticity. Preliminary data suggest that motor-activated auricular VNS may yield greater motor gains than conventional taVNS.

In a related study, functional magnetic resonance imaging (fMRI) was used to compare unilateral and bilateral taVNS in chronic stroke patients.[52] Ipsilesional stimulation produced the most robust activation in motor-relevant brain regions, supporting the rationale for site-specific targeting.

Future priorities include large-scale trials, parameter optimization, and long-term efficacy assessment. If validated, nVNS could become a transformative adjunct to conventional stroke rehabilitation, broadening access and improving outcomes worldwide.

Headache

VNS has emerged as a potential treatment for headache disorders, particularly migraines and cluster headaches, with non-invasive approaches such as tcVNS and taVNS receiving significant attention. The gammaCore device, FDA-approved for both acute and preventive cluster headache treatment and acute migraine relief in adults, delivers transcutaneous cervical VNS, modulating vagal activity to provide therapeutic benefits.[53]

tcVNS has been extensively studied, particularly for acute migraine relief and cluster headache treatment. Early studies indicated that tcVNS could reduce pain duration and increase remission rates.[54] A small pilot study found that 22% of participants were pain-free after two hours, similar to the effects of standard abortive migraine medications.[55] A large RCT involving 248 migraine patients, showed that tcVNS was as effective as triptans for acute migraine relief, particularly at 30 m and 60 m, though its effectiveness diminished at 120 m.[35]

For cluster headaches, as summarized in Table 1, tcVNS has shown promising results. An open-label pilot study reported that 47% of acute cluster headache attacks resolved within 11 m, and preventive tcVNS reduced attack frequency.[55] An RCT by Silberstein *et al*.[36] showed 34.2% pain relief at 15 m (vs. 10.6% with sham) among patients with cluster headaches. These results were confirmed in large RCTs, such as the acute treatment of cluster headache (ACT2) trial,[37] supporting tcVNS's efficacy in episodic cluster headaches. Additionally, the PREVA study showed that tcVNS reduced attack frequency in chronic cluster headaches.[38]

The largest RCT for tcVNS in migraine prevention, followed 332 patients over 12 weeks and found no significant difference in migraine frequency reduction between active and sham groups.[39] However, subgroup analyses indicated potential benefits for specific patient profiles.

While less studied, taVNS is emerging as an alternative.[56] One study showed that 1 Hz taVNS significantly reduced headache days in chronic migraine patients, while another demonstrated improvements in migraine frequency, pain intensity, and attack duration, with fMRI suggesting vagally mediated changes in thalamocortical activity.[57]

While current research supports VNS for migraines and cluster headaches, several gaps remain. Large-scale RCTs are needed to optimize stimulation parameters for both tcVNS and taVNS. Neuroimaging studies using fMRI and electroencephalography could clarify the mechanisms of VNS in pain processing, and machine learning could identify patient subgroups most likely to benefit from VNS. Additionally, comparative effectiveness trials against standard treatments, such as triptans and calcitonin gene related peptide inhibitors, would provide valuable insights.

Future research should explore whether VNS combined with existing therapies improves outcomes and assess long-term safety, durability, and cost-effectiveness. Investigating VNS for other headache types, such as tension-type and post-traumatic headaches, could further expand its clinical applications.

The growing body of research highlights VNS as a promising non-pharmacologic intervention for both acute and preventive treatment of migraines and cluster headaches. tcVNS has the most robust evidence, while taVNS offers potential benefits through its effects on central pain pathways. Refining stimulation protocols, advancing neuroimaging, and adopting personalized treatment approaches will be key to maximizing VNS's clinical utility in headache management.

PD

PD is the second most prevalent neurodegenerative disorder, characterized by the progressive degeneration of nigrostriatal dopamine-producing neurons. As the disease progresses, it affects broader neural networks, leading to both motor and non-motor symptoms.[58] Neuromodulation techniques such as deep brain stimulation, transcranial magnetic stimulation, and transcranial direct current stimulation have been explored as adjunctive treatments but face limitations in targeting deep brain structures.[59] VNS offers a unique advantage by modulating cholinergic and noradrenergic pathways via the nucleus tractus solitarius, influencing broader circuits involved in motor control.[60,61]

Preclinical studies in PD models suggest that VNS may improve motor function, reduce neuroinflammation, decrease alpha-synuclein accumulation, and enhance brain-derived neurotrophic factor, potentially protecting neurons in key regions like the substantia nigra and locus coeruleus.[40,62] Emerging evidence, as summarized in Table 1, also supports the therapeutic potential of non-invasive VNS, particularly taVNS, although findings remain preliminary.

TaVNS, which targets the auricular branch of the vagus nerve, has been shown to be safe, with minor side effects such as ear discomfort and tingling.[63,64] While early studies suggest that taVNS may improve motor symptoms, most have been limited to single-session stimulations, and clinical evidence in PD remains sparse.[65,66] Multiple studies have shown that taVNS activates vagal afferents and influences autonomic functions.[67–69] However, efficacy results are inconsistent. For instance, a double-blind randomized trial found no significant overall motor improvement after ten days of taVNS, though some reductions in bradykinesia and tremors were noted.[70] Another study reported decreased tremor amplitude after auricular VNS.[71]

tcVNS has also been evaluated in PD, particularly for gait. Early trials have shown benefits in step length, velocity, and stride variability.[72] A randomized, double-blind trial by Mondal *et al*.[73] found that tcVNS over 30 days significantly improved gait parameters and Unified Parkinson's Disease Rating Scale-III scores. Farrand *et al*.[41] observed improved executive function but no significant motor improvements after eight weeks of taVNS. Abouelmagd *et al*.[42] reported no motor benefits, though there were mild improvements in sleep and mood. A recent meta-analysis by Song *et al*.[43] found no consistent motor benefits but noted some cognitive improvements and emphasized the need for standardized protocols.

In conclusion, while both taVNS and tcVNS show promise for improving motor symptoms in PD, research is still in its early stages. Studies to optimize stimulation protocols, including treatment duration, frequency, and dosage, are needed to determine the long-term efficacy and safety of VNS in PD management.

AD

AD is the most common form of dementia, with global prevalence projected to rise from 50 million cases in 2019 to 152 million by 2050.[74] AD is characterized by the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles of tau protein, leading to neuronal dysfunction, synaptic loss, and progressive cognitive decline. These pathological changes contribute to neuroinflammation, impaired synaptic plasticity, and metabolic dysregulation, disrupting memory formation and executive function.[75–78] Given the limited efficacy of current pharmacological treatments, alternative approaches targeting neuroinflammation, synaptic integrity, and neuronal survival are being explored to slow disease progression.[79]

One such approach is transcutaneous VNS, a non-invasive neuromodulation technique that has shown promise in mitigating AD-related pathology. Transcutaneous VNS may exert therapeutic effects by enhancing neuroplasticity, reducing Aβ accumulation, modulating neuroinflammation, and supporting neuronal metabolism via astrocyte activation. An RCT in patients with mild cognitive impairment, summarized in Table 1, demonstrated significant cognitive improvements following taVNS, as measured by the Montreal Cognitive Assessment, Pittsburgh Sleep Index, and Boston Naming Test. Wang *et al*.[44] also found that taVNS significantly improved memory function and delayed cognitive decline in mild cognitive impairment patients.

Preclinical studies further support the therapeutic potential of taVNS in AD. In APP/PS1 mouse models, taVNS enhanced spatial memory and learning while reducing Aβ burden and neuroinflammatory markers like IL-1β and IL-18. These effects were mediated via the P2X7R/NLRP3/Caspase-1 signaling pathway, suggesting that taVNS suppresses microglia-driven neuroinflammation.[80] Additionally, taVNS has been shown to improve object recognition and memory persistence while shifting microglial cells from a neurodestructive to a neuroprotective state, further enhancing central anti-inflammatory effects.[81]

In postoperative animal models, taVNS alleviated cognitive deficits by activating cholinergic anti-inflammatory pathways in the basal forebrain and hippocampus. It also reduced apoptotic proteins (cleaved caspase-3) and necrotic markers (p-MLKL), suggesting a role in neuronal survival.[82]

Despite these encouraging findings, further research is needed to establish the long-term efficacy and safety of nVNS in AD. Large-scale clinical trials should optimize stimulation parameters and explore its broader neuroprotective mechanisms. If validated, nVNS could emerge as a novel, non-invasive therapeutic strategy for slowing cognitive decline in AD.

Limitations

Despite its promising potential, several limitations hinder the clinical adoption of nVNS. A major challenge is the heterogeneity of study designs, particularly regarding stimulation parameters (e.g., frequency, intensity, duration), which complicates protocol standardization and data comparison. Most trials have small sample sizes and short follow-up periods, limiting both the generalizability and long-term understanding of nVNS efficacy. While initial findings suggest benefits in conditions like depression, PD, and AD, the evidence remains preliminary, and the durability of effects is unclear. Additionally, although adverse events are generally mild (e.g., ear tingling or discomfort), long-term safety data, especially in vulnerable populations, are lacking. Another significant limitation is the absence of validated biomarkers or predictors of treatment response, making patient selection difficult. Finally, the mechanistic understanding of nVNS remains incomplete, with limited insights into how it modulates neural circuits, inflammation, or neuroplasticity. Most studies focus on clinical outcomes without exploring the underlying biological pathways. Addressing these limitations is crucial for advancing nVNS as a reliable therapeutic option in neurological and psychiatric care.

Future directions

To enhance the clinical utility of nVNS, future research should focus on standardizing protocols, particularly regarding stimulation parameters, to improve reproducibility and comparability across studies. Large-scale, multicenter trials with extended follow-up periods are essential to establish the long-term efficacy and safety of nVNS, particularly in vulnerable populations. The development and validation of predictive biomarkers or response indicators will be critical for optimizing patient selection and personalizing treatment. Mechanistic studies that explore how nVNS modulates neural circuits, inflammatory pathways, and neuroplasticity are essential to deepen our understanding and refine therapeutic approaches. Additionally, integrating multimodal assessments—such as neuroimaging, electrophysiology, and biochemical markers—can provide valuable insights into treatment mechanisms and outcomes. Collaborative efforts among clinicians, neuroscientists, and engineers will be key to developing next-generation devices with adaptive stimulation capabilities. Addressing these research directions will be crucial for translating nVNS from an experimental intervention into a reliable clinical tool in neuropsychiatric care.

Conclusions

nVNS represents a paradigm shift in neuromodulation, offering a safe, accessible, and non-pharmacological alternative for a wide range of neurological and psychiatric conditions. From acute and preventive treatment of migraine and cluster headaches to emerging applications in PD and AD, nVNS has demonstrated promising therapeutic potential by modulating autonomic, inflammatory, and neuroplastic pathways. The cumulative evidence from preclinical models and clinical trials supports its ability to influence key neural circuits underlying pain, cognition, and motor control.

Despite these advances, the widespread clinical integration of nVNS remains limited by heterogeneous study designs, inconsistent stimulation protocols, and insufficient long-term data. A clearer understanding of its mechanisms—supported by neuroimaging, electrophysiology, and biomarker development—is essential for optimizing treatment parameters and guiding personalized applications. As next-generation devices with closed-loop and adaptive capabilities evolve, and interdisciplinary collaborations expand the frontiers of research, nVNS is poised to become a cornerstone in the treatment landscape for neuropsychiatric disorders.

In summary, nVNS holds transformative potential as a non-invasive, patient-friendly, and mechanistically versatile therapy. Realizing this potential will depend on rigorous, large-scale trials, mechanistic investigations, and precision medicine approaches that tailor neuromodulation to individual patient profiles. With continued innovation and validation, nVNS may soon redefine standards of care in neurology and psychiatry.

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Author contributions

Study conceptualization and design (KT, SS), literature search (KT, MA), data organization (SS, AR), drafting of the initial manuscript (KT, SS), manuscript revision and editing (KT, MA, SI, MH, FA), critical content review (SS), project coordination (WA), and study supervision and final approval (WA). All authors reviewed and approved the final manuscript.

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