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Review Article

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Exploring the Therapeutic Potential of Non-Invasive Vagus Nerve Stimulation: A Scoping Review

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Abstract

Background: The vagus nerve, a key element of the parasympathetic nervous system, regulates vital processes such as heart rate, digestion, and immune function. Non-invasive Vagus Nerve Stimulation (nVNS) techniques, including transcutaneous auricular (taVNS) and cervical (tcVNS) methods, have emerged as promising alternatives to invasive stimulation. These approaches show potential in treating neurological, psychiatric, and inflammatory disorders. This scoping review evaluates the therapeutic potential of nVNS, synthesizing evidence on its efficacy, applications, and research gaps. In this scoping review, a systematic literature search was performed in PubMed, Scopus, Cochrane Library, and Google Scholar using terms like "non-invasive vagus nerve stimulation", "taVNS", and "tcVNS". Studies exploring nVNS applications in psychiatric, neurological, and inflammatory disorders were included, focusing on clinical outcomes, protocols, and therapeutic impacts. nVNS demonstrates promise in autonomic modulation, reducing symptoms of treatment-resistant depression, anxiety, and inflammatory conditions like rheumatoid arthritis and Crohn's disease. It also shows potential in managing migraines, cluster headaches, and aiding post-stroke rehabilitation. However, variability in study designs and stimulation protocols limits definitive conclusions. Non-invasive vagus nerve stimulation is a promising non-pharmacological therapy with diverse applications. Standardized large-scale clinical trials are required to optimize stimulation parameters, ensure long-term safety, and develop robust therapeutic guidelines.

Keywords: Depression, Migraine disorders, Parasympathetic nervous system, Search engine, Stroke rehabilitation, Vagus nerve, Vagus nerve stimulation

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Introduction

The vagus nerve, a key component of the parasympathetic nervous system, plays a crucial role in regulating a wide range of physiological processes, including heart rate, digestion, respiratory rate, and inflammatory response. As such, Vagus Nerve Stimulation (VNS) has garnered significant interest in recent years for its potential therapeutic applications across various medical fields. Traditionally, VNS was administered through an invasive surgical procedure that involved implanting an electrode around the vagus nerve in the neck, which was primarily used for treating refractory epilepsy and depression (1). However, due to the invasive nature and associated risks of surgical VNS, recent advancements have led to the development of nVNS techniques that offer a safer, more accessible alternative (2). Non-invasive methods, which primarily include transcutaneous auricular Vagus Nerve Stimulation (taVNS) and transcutaneous cervical Vagus Nerve Stimulation (tcVNS), have shown promising results in a variety of conditions, expanding their potential use far beyond neurological disorders.

The mechanism of action behind VNS lies in its ability to modulate the Autonomic Nervous System (ANS) and influence neuroinflammatory processes (3). Stimulation of the vagus nerve activates afferent fibers that project to the nucleus tractus solitarius in the brainstem, which then interacts with several brain regions involved in mood regulation, pain processing, and inflammatory response (4). Through the cholinergic anti-inflammatory pathway, VNS has been shown to reduce the release of pro-inflammatory cytokines, which can be particularly beneficial in conditions characterized by chronic inflammation, such as rheumatoid arthritis, inflammatory bowel disease, and certain cardiovascular diseases (5). Additionally, by modulating ANS balance, VNS has demonstrated potential in managing conditions associated with autonomic dysfunction, including migraine, post-traumatic stress disorder, and even obesity (6,7).

Non-invasive VNS, with its ease of application and lower side-effect profile, has enabled researchers to explore the potential of VNS in a broader range of conditions, including psychiatric, neurological, and inflammatory disorders. In the realm of psychiatric applications, for example, studies have found that nVNS may help alleviate symptoms in patients with treatment-resistant depression and anxiety disorders by enhancing neuroplasticity and regulating mood-related brain circuits (8). Neurological applications have similarly expanded, with evidence suggesting that nVNS can serve as a non-pharmacological option for migraine and cluster headache management (9,10). Beyond these areas, nVNS is also being investigated for its potential role in modulating cognitive function and improving outcomes in post-stroke rehabilitation, where it could facilitate neurorehabilitation by promoting neurogenesis and motor recovery (11).

Despite the growing body of evidence supporting the efficacy of nVNS, there are several challenges and limitations associated with its application. The heterogeneity of study designs, variability in stimulation parameters, and differences in targeted patient populations have resulted in mixed findings and make it challenging to draw definitive conclusions about its clinical utility (12). Furthermore, while nVNS devices are generally well tolerated, some patients report discomfort, and optimal stimulation parameters are still under investigation (13). The need for standardized protocols and well-designed, large-scale clinical trials is crucial to establish the safety and efficacy of nVNS and to better understand its therapeutic mechanisms (14).

The present scoping review aims to synthesize current evidence on the therapeutic potential of non-invasive VNS across a range of medical conditions. By exploring recent studies and highlighting emerging trends, this review seeks to provide a comprehensive overview of the current landscape and to identify gaps in knowledge that warrant further investigation. Understanding the breadth and limitations of nVNS applications can guide future research efforts and inform clinical practice, potentially leading to more personalized and effective interventions (15).

Materials and Methods

Study design

This scoping review followed the methodological framework outlined by Arksey and O'Malley for conducting scoping studies, with enhancements proposed by Levac *et al*, to explore the therapeutic potential of nVNS. The review aimed to map the

current evidence, identify key areas of application, and highlight gaps in research, consistent with the exploratory nature of scoping reviews (16,17).

Literature search strategy

The review was conducted, and the study included data from the past 10 years, covering the period from 2012 to 2023, utilizing a comprehensive search across PubMed, Scopus, Cochrane Library, and Google Scholar to identify relevant peer-reviewed and gray literature. The search employed keywords such as "non-invasive vagus nerve stimulation", "transcutaneous auricular vagus nerve stimulation (taVNS)", "transcutaneous cervical vagus nerve stimulation (tcVNS)", "neuroinflammation", "autonomic regulation", and "cholinergic anti-inflammatory pathway". Boolean operators like "AND" and "OR" and truncation techniques were applied to refine the search strategy. Studies published in English involving human participants were included, while conference abstracts, editorials, and opinion pieces were excluded to maintain the review's focus and rigor (18).

Inclusion criteria

Studies were included if they examined the therapeutic applications of nVNS across various conditions, including psychiatric, neurological, inflammatory, and cardiovascular disorders. Eligible studies focused on key outcomes such as symptom alleviation, modulation of the autonomic nervous system, reduction of inflammatory markers, and functional improvements. Additionally, they provided detailed descriptions of nVNS protocols, including the type of device used, stimulation parameters, and the application site (auricular or cervical). The study designs considered for inclusion encompassed Randomized Controlled Trials (RCTs), cohort studies, case-control studies, and case series that employed robust methodologies (19,20).

Exclusion criteria

Studies were excluded if they focused exclusively on invasive VNS techniques, did not report on the therapeutic outcomes of interest, lacked sufficient methodological detail or outcome measures, or were non-human studies. Additionally, publications in languages other than English were also excluded (21,22).

Bias mitigation

To reduce potential bias, studies with possible conflicts of interest—particularly those funded by manufacturers of nVNS devices—were carefully assessed for transparency and methodological rigor. Priority was given to independent, peer-reviewed research, while studies lacking clear or adequate control mechanisms were excluded from the analysis. Table 1 presents the Cochrane Risk of Bias assessment for the included studies.

Data extraction

Comprehensive data were systematically extracted from each selected study to facilitate a thorough evaluation and synthesis of findings. This included detailed information on the study design (*e.g.*, RCTs, observational studies), methodological approach, and total sample size. In addition, participant demographics were carefully recorded, encompassing variables such as age, gender distribution, and specific medical conditions or diagnoses relevant to the study population.

Critical aspects of the nVNS protocol were meticulously documented. These included the type and model of the stimulation device, the anatomical site of stimulation (*e.g.*, cervical or auricular branches of the vagus nerve), stimulation parameters (such as pulse width, frequency, and intensity), treatment frequency (number of sessions per day or week), and overall duration of the intervention period.

Furthermore, outcome measures were extracted with a focus on both efficacy and safety. This involved recording primary and secondary clinical endpoints, such as symptom improvement scores, functional outcomes, quality-of-life measures, and the incidence and severity of any reported adverse events. These results were analyzed in the context of the conclusions drawn by the original study authors, with particular attention to the demonstrated therapeutic potential of nVNS across different patient populations and clinical settings (23).

Table 2 provides a comprehensive overview of the key characteristics of the included studies, while table 3 details participant enrollment numbers, retention

Table 1. Cochrane risk of bias table of included studies

Author, Year	Random allocation	Allocation concealement	Selective reporting	Other bias	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	Score
Michiaki Nagai, *et al*, 2012	+	+	+	+	+	+	+	7
Jennifer A. Clancy, *et al*, 2014	+	-	+	+	+	-	+	5
Roberta Sclocco, *et al*, 2017	+	-	+	+	-	-	+	4
M. De Couck, *et al*, 2017	+	-	+	+	-	-	+	4
Diego Antonino, *et al*, 2017	+	-	+	+	-	-	+	4
Jessica Stowell, *et al*, 2019	+	-	+	+	-	-	+	4
Harris Fisher, *et al*, 2018	+	-	+	+	+	-	+	5
Rachel Staley, *et al*, 2020	+	?	+	+	+	-	+	5
Matjaz Sinkovec, *et al*, 2021	-	-	+	+	-	-	+	3
Ronald G. Garcia, *et al*, 2022	+	?	+	+	+	-	+	5
Kristin Kaduk, *et al*, 2023	+	-	+	+	+	-	+	5

+: Low risk of bias, -: High risk of bias, ?: Unclear risk of bias.

Table 2. Characteristics of the included studies

Author & Year	Study design	(Group-I)	(Group II)	Outcome variables (assessment tools)	Result
Michiaki Nagai, *et al*, 2012	Randomised control trial	The ear clip electrode was positioned on the tragus in the active group. The stimulation parameters included a pulse width of 200 µs and a pulse frequency of 20 *Hz*. The stimulation intensity was adjusted to 1 *mA* below the level of discomfort	In the sham group, the ear clip electrode was placed on the earlobe, an area lacking vagal innervation. The stimulation parameters consisted of a pulse width of 200 *µs* and a pulse frequency of 20 *Hz*. The stimulation intensity was set to 1 *mA* below the discomfort threshold	Central aortic systolic pressure (A-pulse CASPro device), Systolic blood pressure, diastolic blood pressure, heart rate	The active group demonstrated notable reductions in CASP, SBP, DBP, and HR, whereas the sham group showed significant increases in these parameters. The changes observed between the active and sham groups were statistically significant. No side effects associated with the device were reported. tVNS effectively led to an acute reduction in afterload among elderly AHF patients. Non-invasive LLTS was found to be a safe method for lowering afterload in AHF
Jennifer A. Clancy, *et al*, 2014	Randomised control trial	Electrodes were positioned on both the inner and outer surfaces of the ear's tragus. Active tVNS (n=34) was administered continuously for 15 minutes using a pulse width of 200 µs and a pulse frequency of 30 *Hz*. The amplitude was set based on the sensory threshold, ranging from 10 to 50 *mA*	Sham tVNS (n=14) was conducted by attaching the electrodes to the tragus and gradually increasing the amplitude until the participant indicated perceiving a sensation	Heart rate variability (HRV) was measured using a three-lead ECG, respiration was monitored using a piezo-electric transducer, and microneurography was employed to assess muscle sympathetic nerve activity	Active tVNS was associated with an increase in HRV in healthy individuals. A significant reduction in muscle sympathetic nerve activity was observed during tVNS. Both systolic and mean blood pressure rose during tVNS. Further research is needed to explore the long-term effects of tVNS on HRV

Contd. table 2.

Roberta Sclocco, *et al*, 2017	Randomised crossed over design	Participants underwent RAVANS stimulation in the left ear using ergonomically designed Ag/AgCl electrodes. The stimuli were rectangular pulses with a pulse width of 450 µs and a duration of 1 second, delivered at a frequency of 25 *Hz* during each exhalation phase. Respiratory gating was achieved by using a pneumatic belt to monitor the subjects' breathing, which controlled the timing of the stimulation	-	HRV (ECG), Respiration (Pneumatic belt)	Moderate-intensity RAVANS enhances cardiovagal tone, while it decreases sympathetic tone during paced breathing. All participants tolerated RAVANS without experiencing discomfort. Medium-intensity RAVANS resulted in the greatest increase in parasympathetic outflow. Sympathetic tone was reduced during both low and medium-intensity RAVANS. Preliminary findings indicate its potential for treating hypertension
M. De Couck, *et al*, 2017	Randomised crossed over design	Transcutaneous vagus nerve stimulation (t-VNS; Cerbomed, Germany) was administered through electrical stimulation of the auricular branch of the vagus nerve (ABVN) on either the left or right ear while the participant was seated. t-VNS delivered rectangular pulses of 250 *µs* duration to the cymba conchae area of the outer ear using double ball point electrodes. The stimulation protocol involved alternating 30-*s* pulse series, followed by a 30-*s* pause. The frequency of the stimulation was set to 25 *Hz* during the active session, while the sham session involved no stimulation. t-VNS was applied for 10 *min* to either the left or right ear at 25 *Hz*	t-VNS delivers rectangular pulses with a duration of 250 *µs* to the cymba conchae region of the outer ear using double ball point electrodes. The protocol involved alternating pulse series lasting 30 *s*, followed by a 30-*s* pause. t-VNS was applied at a frequency of 25 *Hz* to the right ear for a duration of 1 *hr*	HRV (ECG), Abdominal respiration (flexible belt)	Right ear t-VNS significantly increased SDNN after 10 *min*, while prolonged t-VNS (1 *hr*) had modest effects on HRV. Overall, no significant changes in HRV were observed in the entire sample following t-VNS. Women exhibited more consistent changes in SDNN compared to men. No significant differences in HRV were found between left and right ear t-VNS. Overall, the effects of t-VNS on HRV were limited
Diego Antonino, *et al*, 2017	Randomised placebo-controlled trial, crossover study	Active tVNS: Electrical stimulation was applied continuously for 15 *min* with a pulse width of 200 *µs* and a pulse frequency of 30 *Hz*. The stimulation amplitude was varied between 10 and 50 *mA*. Sham: Electrodes were placed on the tragus of the ear, but no electrical current was delivered. Transcutaneous Lobe Stimulation (tLS): Electrodes were positioned on the ear lobe, and electrical stimulation was applied using the same parameters as the active tVNS. The Transcutaneous Electrical Nerve Stimulation (TENS) device included a compact stimulation unit and modified surface electrodes, which were placed bilaterally on the inner and outer surfaces of the tragus for both active and sham-T protocols, and on the ear lobe during the tLS protocol	-	HR and Arterial BP (finger photoplethy-smography), Brachial arterial BP (Digital sphygmo-manometer) HRV (ECG)	Active tVNS enhanced spontaneous cardiac baroreflex sensitivity (cBRS), while no changes were observed in cBRS during the sham-T or tLS protocols. A slight decrease in heart rate was noted during active tVNS. These effects were specific to the stimulation of the auricular branch of the vagus nerve
Jessica Stowell, *et al*, 2019	Crossover study	Five stimulation sessions were conducted, where RAVANS at frequencies of 2, 10, 25, 100 *Hz*, or Sham stimulation were applied during each visit. Custom-designed, ergonomically-shaped electrodes were positioned on the subjects' left cymba concha. Monophasic rectangular pulses (300 *µs* pulse width, 1 s duration) were administered via a Urostim device, with a short 0.8 s delay following peak inhalation. Respiratory gating for the stimulation was achieved by monitoring respiration using a pneumatic belt around the subject's lower thorax. The respiratory signal was captured by a device connected to a laptop, and computer software was used to detect end-inhalation in real-time. Electrical stimulation was applied to the ear during the exhalation phase of the respiratory cycle	-	Blood pressure (Finometer device)	RAVANS shows frequency-dependent effects on blood pressure regulation. Stimulation at 100 *Hz* led to a significant decrease in systolic blood pressure, with an average reduction ranging from -5.06 to -10.55 *mmHg*. No notable effects were observed with other stimulation frequencies

Contd. table 2.

Harris Fisher, *et al*, 2018	Randomised crossed over design	Participants participated in three stimulation sessions, where they received either sham, low-intensity, or medium-intensity stimulation in a randomized sequence. Electrodes were positioned on the left ear, specifically on the cymba concha and below the antihelix, areas known to be innervated by the auricular branch of the vagus nerve. Biphasic electrical stimulation was applied at 25 *Hz* (1-*s* duration, 15 *ms* pulse width), synchronized with exhalation. The current intensity was adjusted to induce a mild to moderate, non-painful sensation. In the sham condition, the current generator was turned off	-	Blood pressure (Finometer device)	RAVANS significantly reduced systolic blood pressure in hypertensive patients, medium intensity RAVANS showed lower SBP increase than sham, Nine out of ten subjects responded positively to RAVANS, both low and medium intensity maintained controlled SBP during recovery, Recovery phase showed significant SBP decrease after RAVANS
Rachel Staley, *et al*, 2020	Randomised control trial	Exhalatory-gated RAVANS was delivered at a frequency of 25 *Hz* (monophasic rectangular pulses, 300 *μs* pulse width; 1 *s* duration) with a UROstim transcutaneous electrical stimulator. tVNS electrodes were place on the left ear, specifically on the surface of the cymba concha, a vagal-innervated auricular region. Stimulation amplitude was individually calibrated to a moderate, nonpainful intensity	Sham stimulation was delivered with the current generator turned off	HRV (ECG), Blood pressure	RAVANS therapy enhances HF-HRV power during recovery phases and reduces heart rate during stimulation. It also leads to an increase in Average RR intervals and RMSSD values. No notable changes in blood pressure were observed, and the effects persisted for up to 10 days after stimulation. Daily sessions of RAVANS, lasting 30 *min* over five consecutive days, promote parasympathetic activity and improve cardiovagal function
Matjaz Sinkovec, *et al*, 2021	Open-Label Pilot study	Each session included a 60-minute resting phase, followed by a 15-minute phase for autonomic nervous system testing (ANST). In the first session, a sham (placebo) stimulation was administered, while the second session involved actual stimulation. The stimulation was delivered using a transcutaneous electrical nerve stimulator applied to the skin inside the right tragus through two silver electrodes mounted on clips. A constant current was used, featuring 1 *ms* monophasic rectangular waveforms at a frequency of 20 *Hz*. The intensity was adjusted individually to a barely perceptible level, typically remaining below 150 *μA*	-	Heart rate (6 Lead ECG), BP (Vascular unloading method from 3 and 4th finger of left hand), cardiac function parameter (impedance cardiography)	A marked reduction in left ventricular contractility and output was observed, along with a slower heart rate and a significant decrease in left ventricular workload. Blood pressure and peripheral resistance parameters showed an increase, while the overall discomfort index rose during stimulation. No notable changes were detected in heart rate variability measures
Ronald G. Garcia, *et al*, 2022	Crossover study	Exhalatory-gated RAVANS was applied to the left ear. Each session included a 10-*min* baseline phase, a 30-*min* stimulation phase, and a 10-*min* post-stimulation phase. Participants remained seated in an upright posture throughout the session. The RAVANS stimulation was delivered at varying frequencies (2 *Hz*, 10 *Hz*, 25 *Hz*, 100 *Hz*, or sham) in a randomized sequence across sessions	-	Arterial blood pressure (Finometer device), heart functioning (ECG), Pulse rate (Piezo pulse transducer)	RAVANS at a frequency of 100 *Hz* effectively lowered heart rate in individuals with hypertension. A significant decrease in both diastolic blood pressure and mean arterial pressure was observed. In contrast, lower frequencies did not produce substantial effects. The impact was particularly prominent among Black hypertensive participants, and there were indications of potential differences in heart rate responses between males and females

Contd. table 2.

Kristin Kaduk, *et al*, 2023	Randomised crossed over design	The NEMOS® device was utilized to activate the auricular branch of the vagus nerve. For taVNS, the electrode was positioned at the cymba conchae. During sham stimulation, the electrode was inverted and applied to the earlobe	-	HR, R peak detection and cardiovascular indices (ECG)	taVNS does not robustly alter vagally-mediated HRV in humans, Changes in HR and HRV are independent of stimulation side

Table 3. Study participant enrollment and retention details

Author and Year	Eligible for illusion	Excluded	Number allocated		Excluded post allocation	Lost to follow up	Included in final analysis	
			N1	N2	-	-	N1	N2
Michiaki Nagai, *et al*, 2012	45	23	11	11	6	0	8	8
Jennifer A. Clancy, *et al*, 2014	48	0	34	14	-	0	34	14
Roberta Sclocco, *et al*, 2017	12	-	12	-	-	-	12	-
M. De Couck, *et al*, 2017	60	0	30	30	-	0	30	30
Diego Antonino, *et al*, 2017	13	0	13	-	-	0	13	-
Jessica Stowell, *et al*, 2019	12	-	12	-	-	0	12	-
Harris Fisher, *et al*, 2018	18	-	18	-	-	-	10	-
Rachel Staley, *et al*, 2020	20	0	12	8	-	5	8	7
Matjaz Sinkovec, *et al*, 2021	15	0	15	-	-	-	15	-
Ronald G. Garcia, *et al*, 2022	20	0	20	-	-	0	20	-
Kristin Kaduk, *et al*, 2023	38	2	36	-	-	-	36	-

rates, and any reported attrition, thereby supporting the evaluation of study quality and the reliability of findings.

Review registration and ethical approval

The review was not prospectively registered, as is typical for scoping reviews. Ethical considerations were adhered to, focusing solely on publicly available data (24).

Results

The process of literature search and study selection was systematically documented using the PRISMA flow diagram. This diagram outlines the number of records identified, screened, assessed for eligibility, and ultimately included in the review, with reasons

for exclusion noted at each stage. Extracted data were synthesized and organized into tables that summarize key aspects of each study, including design, intervention protocols, outcome measures, and main findings.

Figure 1 presents the PRISMA flow diagram illustrating the selection process. The final set of included studies encompassed a range of research designs: three randomized controlled trials (RCTs), four randomized crossover design studies, one randomized placebo-controlled crossover trial, two crossover studies, and one open-label pilot study.

Discussion

The findings of this scoping review highlight the therapeutic potential of nVNS across a range of applications, including autonomic modulation, inflammatory response attenuation, and mental health improvement. By synthesizing results from studies spanning over a decade, key insights into the mechanisms, clinical applications, and research gaps have been identified.

Mechanisms of action and physiological impact

The physiological basis of nVNS has been extensively investigated, with key contributions from Clancy *et al* and Antonino *et al*. Clancy and colleagues examined how nVNS modulates Heart Rate Variability (HRV), demonstrating its potential to influence the autonomic nervous system by enhancing parasympathetic activity and reducing sympathetic overdrive. This modulation of autonomic tone is crucial for various conditions, including cardiovascular disorders, where maintaining a balanced autonomic function is vital. Antonino *et al* further confirmed these findings, highlighting transcutaneous Vagus Nerve Stimulation (tVNS) and its ability to strengthen parasympathetic

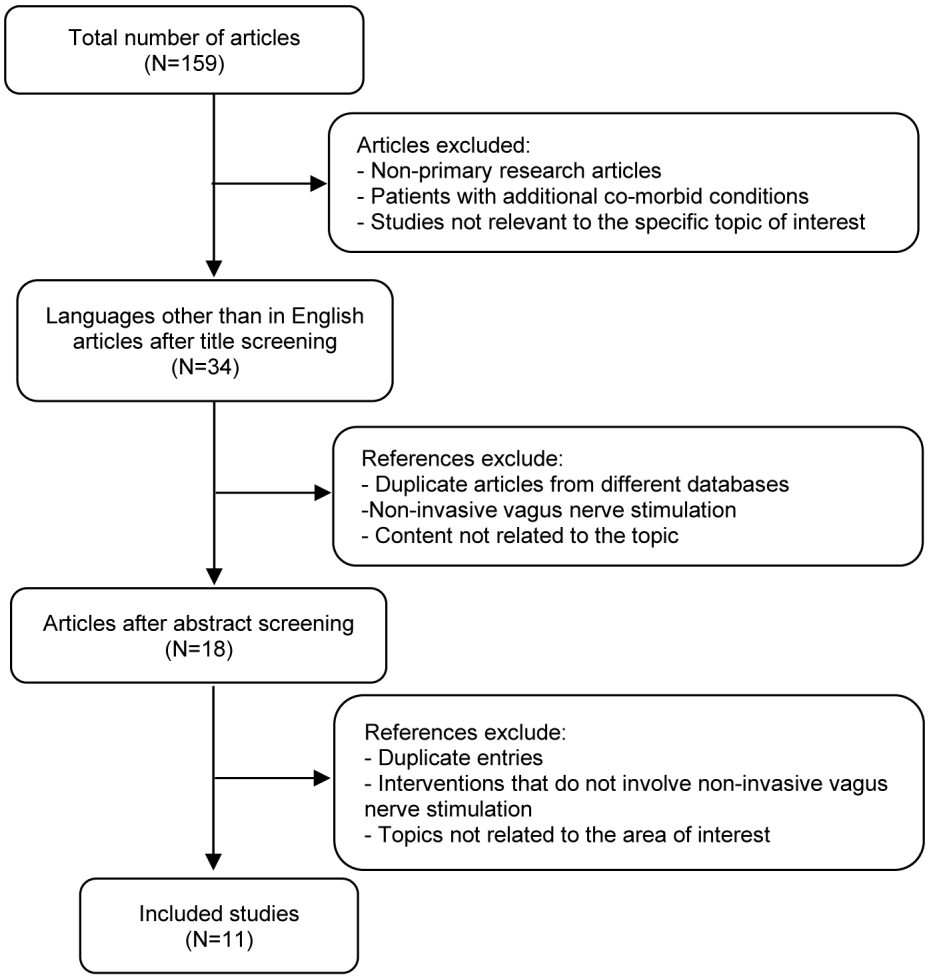

Figure 1. PRISMA flow diagram for selection of articles.

activity. By reducing sympathetic dominance, tVNS offers therapeutic potential for conditions such as anxiety and stress, which are often linked to autonomic dysregulation. Additionally, nVNS and tVNS have shown promising effects in treating migraine and cluster headaches, providing a non-pharmacological option for managing these debilitating conditions that involve altered autonomic regulation (25,26).

Applications in neurology and psychiatry

The potential for nVNS to influence brain function has been explored in depth, particularly in the context of neurological and psychiatric disorders. Sclocco *et al* utilized advanced neuroimaging techniques to investigate the effects of nVNS on brain regions responsible for pain processing. Their study identified significant changes in activity within the anterior cingulate cortex and insula, areas known to play pivotal roles in pain perception and emotional regulation. These findings suggest that nVNS could be an effective intervention for managing chronic pain conditions such as migraines and fibromyalgia, where traditional treatment options often fall short (27).

Additional studies by De Couck *et al* and Nagai *et al* expanded on these findings by examining the interaction between nVNS and the Hypothalamic-Pituitary-Adrenal (HPA) axis. Their research revealed that nVNS not only reduces sympathetic activity, but also helps regulate the HPA axis, a critical system involved in stress response and inflammatory processes. By attenuating overactivation of the HPA axis, nVNS demonstrates the potential to alleviate stress-induced physiological damage and control inflammatory pathways. These findings highlight nVNS as a promising approach to managing systemic inflammatory diseases and stress-related disorders, such as chronic inflammation, anxiety, and Post-Traumatic Stress disorder (PTSD) (28,29).

In the realm of psychiatry, Stowell *et al* explored the impact of nVNS on mood regulation. Their work demonstrated how nVNS influences neural circuits involved in emotional processing, providing evidence for its application in mood disorders like depression and anxiety. This aligns with the findings of Garcia *et al*, who emphasized the role of nVNS as an adjunctive therapy for depression. The study highlighted how nVNS complements conventional pharmacological treatments by modulating neural pathways associated with emotional dysregulation, thereby offering potential benefits for patients with treatment-resistant depression. This ability to target specific neural networks highlights the versatility of nVNS in addressing psychiatric conditions where therapeutic needs remain unmet (30,31).

Anti-inflammatory and immunomodulatory effects

The anti-inflammatory properties of nVNS have been extensively investigated, with studies by Fisher *et al* and Staley *et al* shedding light on its mechanisms. These studies highlight the activation of the cholinergic anti-inflammatory pathway by nVNS, which plays a pivotal role in modulating the immune response. Through this pathway, nVNS effectively reduces the release of pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-alpha) and Interleukin-6 (IL-6). Such findings underscore the therapeutic potential of nVNS in managing chronic inflammatory conditions such as rheumatoid arthritis and Crohn's disease, where inflammation is a central pathological feature (32,33).

Device innovation and technological advances

The advancements in device technology have been instrumental in enhancing the accessibility and effectiveness of nVNS therapies. Sinkovec *et al* highlighted significant progress in the development of wearable nVNS devices, which prioritize user-friendliness and improved therapeutic efficacy. These devices are designed to increase patient compliance by offering non-invasive, portable, and easy-to-use options that can seamlessly integrate into daily routines (34).

More recently, Kaduk *et al* expanded the understanding of nVNS by examining its role in metabolic regulation. Their findings demonstrate a connection between vagus nerve stimulation and metabolic homeostasis, suggesting that nVNS may influence weight management and other metabolic processes. This integrative approach broadens the applicability of nVNS, emphasizing its potential to address both inflammatory and metabolic disorders

through non-invasive means (35).

Kaduk *et al* further explored innovations in device safety and functionality, introducing designs optimized for long-term use across diverse patient populations. These improvements address concerns about prolonged stimulation and potential adverse effects, thereby making nVNS more practical for chronic use in clinical and home settings. Together, these advancements pave the way for broader adoption of nVNS in clinical practice, particularly in managing conditions that require ongoing therapeutic interventions (35).

Research gaps and future directions

Despite significant progress in understanding and implementing nVNS, several critical gaps remain. A recurring limitation in the literature, including studies by Fisher *et al* and Garcia *et al*, is the focus on short-term outcomes. While these studies provide valuable insights into the immediate benefits of nVNS, the long-term sustainability and safety of these effects remain unclear. This lack of longitudinal data limits the ability to fully assess the durability of therapeutic benefits over extended periods (31,32).

Another challenge lies in the variability of stimulation parameters used across studies, such as frequency, intensity, and duration. This inconsistency complicates the establishment of standardized treatment protocols, hindering widespread clinical adoption. Comparative studies examining the efficacy of auricular *vs*. cervical stimulation are also limited, leaving room for ambiguity about which method is more effective for specific conditions.

To address these gaps, future research should prioritize longitudinal studies to evaluate the sustained effects and safety of nVNS over extended periods, spanning months or years. Comparative trials are also essential to determine the relative effectiveness of auricular versus cervical stimulation, which could guide the selection of the most appropriate application for different patient populations. Additionally, expanding the application of nVNS to underserved therapeutic areas, such as pediatric populations and neurodegenerative conditions, holds the potential to uncover new opportunities for its use. By tackling these challenges, future studies can build upon existing evidence to optimize the therapeutic potential of nVNS and broaden its scope in medical practice.

Conclusion

The findings from this scoping review underscore the significant therapeutic potential of nVNS across multiple clinical domains, including autonomic regulation, mental health management, and the modulation of inflammatory responses. The ability of nVNS to influence autonomic nervous system activity presents promising applications in the management of cardiovascular conditions, anxiety, and stress-related disorders. Its positive effects on mental health, particularly in mood disorders such as depression, have been increasingly recognized in recent research. Additionally, the observed anti-inflammatory properties suggest potential benefits in addressing chronic inflammatory conditions.

For allied health professionals, these findings hold practical relevance in broadening therapeutic strategies and integrating nVNS as a complementary modality within multidisciplinary care.

Physiotherapists, occupational therapists, and other allied health practitioners can consider the use of nVNS in rehabilitation programs aimed at enhancing autonomic balance, improving mental well-being, and reducing systemic inflammation. Its non-invasive nature makes it an attractive option for long-term management and patient compliance.

However, the current variability in stimulation parameters—including frequency, intensity, and duration—poses a challenge to widespread clinical adoption. Thus, allied health professionals should advocate for and participate in the development of standardized protocols and clinical guidelines. Furthermore, long-term and large-scale studies are needed to validate the sustained benefits of nVNS and establish its role within routine clinical practice.

Limitations

This scoping review provides an overview of nVNS but has several limitations. The included studies exhibit heterogeneity in design, sample sizes, and methodological quality, complicating definitive conclusions. Variations in stimulation parameters (*e.g.*, frequency, intensity, and duration) further hinder result comparisons. Additionally, many studies lack long-term follow-up, limiting

the assessment of sustained effects and safety. The absence of comparative trials between different nVNS techniques and the exclusion of non-English studies may have omitted relevant research. These factors highlight the need for more rigorous, large-scale, long-term studies.

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Conflict of Interest

Authors declare no conflict of interest.

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