International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	CURRENT STATE OF KNOWLEDGE CONCERNING VAGUS NERVE STIMULATION IN TREATMENT OF MAJOR DEPRESSIVE DISORDER
ARTICLE INFO	Julia Guzowska, Barbara Wołoszyn, Patrycja Rzeźnik, Maciej Sobczyk, Weronika Stachera, Aleksandra Chajnowska, Aleksandra Borowy, Wiktoria Suchcicka, Małgorzata Zach, Julia Stępień. (2025) Current State of Knowledge Concerning Vagus Nerve Stimulation in Treatment of Major Depressive Disorder. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3785
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3785
RECEIVED	20 July 2025
ACCEPTED	01 September 2025
PUBLISHED	03 September 2025
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

CURRENT STATE OF KNOWLEDGE CONCERNING VAGUS NERVE STIMULATION IN TREATMENT OF MAJOR DEPRESSIVE DISORDER

Julia Guzowska *(Corresponding Author, Email: jguzowska779@gmail.com)*
District Medical Centre in Grójec, Piotra Skargi 10, 05-600 Grójec, Poland
ORCID ID: 0009-0004-3515-121X

Barbara Wołoszyn
Independent Public Health Care Facility - A Complex of Facilities in Maków Mazowiecki, Witosa 2, 06-200 Maków Mazowiecki, Poland
ORCID ID: 0009-0009-0386-1205

Patrycja Rzeźnik
Independent Public Health Care Facility - A Complex of Facilities in Maków Mazowiecki, Witosa 2, 06-200 Maków Mazowiecki, Poland
ORCID ID: 0009-0002-9206-7300

Maciej Sobczyk
Medical University of Lublin, 1 Racławickie St., 20-059 Lublin, Poland
ORCID ID: 0009-0004-1810-5916

Weronika Stachera
Medical University of Lublin, 1 Racławickie St., 20-059 Lublin, Poland
ORCID ID: 0009-0003-9927-0667

Aleksandra Chajnowska
Independent Public Healthcare Center No.1 in Rzeszów, Rycerska 4, 35-241 Rzeszów, Poland
ORCID ID: 0009-0003-2826-2926

Aleksandra Borowy
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
ORCID ID: 0009-0001-5542-3225

Wiktoria Suchcicka
National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warszawa, Poland
ORCID ID: 0009-0006-8090-4852

Małgorzata Zach
University Clinical Hospital named after Fryderyk Chopin in Rzeszów, Szopena St. 2, 35-055 Rzeszów, Poland
ORCID ID: 0009-0006-8061-9613

Julia Stępień
Medical University of Lublin, 1 Racławickie St., 20-059 Lublin, Poland
ORCID ID: 0009-0000-6113-9581

ABSTRACT

Introduction and aim: Vagus Nerve Stimulation (VNS), including its non-invasive form transcutaneous auricular VNS (taVNS), has emerged as a promising treatment for Major Depressive Disorder (MDD), particularly treatment-resistant cases. The aim of this review is to provide a comprehensive review of VNS and taVNS, with a focus on their mechanisms, efficacy, and immunomodulatory effects in depression.
Methods: A systematic review of PubMed literature (2020-2025) was conducted using the terms "Depresion," and either "Transcutaneous Auricular Vagus Nerve Stimulation" or "taVNS" or "Vagus Nerve Stimulation" or "VNS" and "depression" or "Major Depressive Disorder" with studies manually screened for relevance and credibility.
Results: VNS modulates the brain's monoaminergic systems by enhancing serotonergic and noradrenergic neurotransmission via afferent vagal projections. It also exerts anti-inflammatory effects by activating cholinergic anti-inflammatory pathways that reduce systemic and central neuroinflammation- which has been suggest as an underlying mechanism for the pathophysiology of depression. VNS also influences the microbiota–gut–brain axis, improving intestinal barrier integrity and restoring gut microbial balance. Dysbiosis may be one of the factors involved in the pathogenesis of depression. TaVNS, targeting the auricular branch of the vagus nerve, activates similar neural circuits and shows comparable antidepressant effects with fewer risks. Clinical trials and meta-analyses support its efficacy, especially when combined with pharmacotherapy.
Conclusion: VNS and taVNS represent effective adjunctive treatments for MDD by modulating neurochemical, immunological, and microbiota-related pathways. Further large-scale, controlled trials are needed to clarify optimal stimulation parameters and long-term outcomes.

KEYWORDS

Vagus Nerve Stimulation, Transcutaneous Auricular Vagus Nerve Stimulation, Depression, Major Depressive Disorder

CITATION

Julia Guzowska, Barbara Wołoszyn, Patrycja Rzeźnik, Maciej Sobczyk, Weronika Stachera, Aleksandra Chajnowska, Aleksandra Borowy, Wiktoria Suchcicka, Małgorzata Zach, Julia Stępień. (2025) Current State of Knowledge Concerning Vagus Nerve Stimulation in Treatment of Major Depressive Disorder. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3785

1. Introduction

Vagus Nerve Stimulation (VNS) is a well-established procedure that delivers constant electrical impulses to the vagus nerve, thereby stimulating it. Stimulation is achieved via an electrode cuffed around the left vagus nerve, connected by a small, flexible lead to a pulse generator that is surgically implanted in the patient's left pectoral region (Austelle, Cox, Wills, & Badran, 2024; Andalib et al., 2023; Kraus et al., 2022). The pulse generator is usually housed in a protective titanium casing. An external programming device allows the clinician to adjust stimulation parameters, including pulse width, frequency, on/off time, time administered and the intensity of the current (mA) (Kraus et al., 2022; Thompson et al., 2021).

The origins of VNS go back to the late 19th century, stemming from the work of neurologist James Leonard Corning, who developed a procedure similar to modern VNS as a preventive treatment for epilepsy. VNS was approved by FDA by the end of the 20th century and was initially used for the treatment of epilepsy. Soon, researchers began to observe incidental findings, particularly improvements in patients' mood, which led to the exploration of VNS as a potential treatment for depression (Austelle et al., 2024). Since then numerous studies have confirmed that VNS can be an effective treatment for depression, including treatment-resistant depression (Austelle et al., 2024; Wang et al., 2021a). As a result, in 2005, the FDA approved VNS for use in patients with treatment-resistant major depressive disorder (MDD) (Wang et al., 2021b).

At the beginning of the 21st century a new non-invasive version of VNS, known as transcutaneous auricular Vagus Nerve Stimulation (taVNS), was developed. TaVNS has also shown promising results in the treatment of depression (Austelle et al., 2024). In light of the rapid development of research on these methods,

this paper aims to aggregate the most recent studies and present the current state of knowledge regarding VNS and taVNS, with particular emphasis on their mechanisms and efficacy in the treatment of depression.

2.Material and methods

A systematic review of scientific articles was conducted using the PubMed database. The terms used for the search included”Vagus Nerve Stimulation" or”Transcutaneous Auricular Vagus Nerve Stimulation", as well as”Depression” or”Major Depressive Disorder". The analysis focused on articles and research papers published from 2020 to 2025. The titles and abstracts were reviewed manually to evaluate their relevance and the source of the article. As this paper is not a meta-analysis, no statistical methods were employed.

3.State of knowledge

The anatomy of vagus nerve

To comprehend the theory behind VNS, it is essential to first explore and understand the role and function of the vagus nerve. The vagus nerve, also known as the tenth cranial nerve, originates in the brainstem and extends through the neck to innervate various organs in the chest and abdomen. It exists on both sides of the body and plays a critical role in the parasympathetic nervous system (Austelle et al., 2024; Kenny & Bordoni, 2025).

Vagus nerve is a mixed nerve, composed of both afferent and efferent fibers. Afferent fibers, which contribute to approximately 80% of its fibers, transmit sensory information from internal organs. These afferents can be divided into three categories: (i) general somatic afferents, which relay sensory input from the skin; (ii) general visceral afferents, which convey signals from the internal organs such as the heart, lungs, esophagus, gaster and intestines; and (iii) special visceral afferents, which are involved in the perception of taste (Patros et al., 2025; Baquiran & Bordoni, 2025). Importantly, some visceral afferent endings of the vagus nerve function as chemoreceptors that detect chemical stimuli from the gastrointestinal lumen (Patros et al., 2025). These endings, along with other components of the vagus nerve, play a key role in the gut–brain axis (Gerges et al., 2024).

The efferent fibers can be divided into two categories: (i) general visceral efferents, which innervate the smooth muscle and glands of the thoracic and abdominal viscera, pharynx and larynx; (ii) special visceral efferents, which innervate the striated muscle of the pharynx and larynx (Patros et al., 2025).

The vagus nerve transmits information to or from the following brainstem nuclei: the nucleus ambiguous (the efferent motor fibers), the dorsal nucleus of vagus nerve (parasympathetic efferent motor fibers), the solitary nucleus (the afferent visceral sensory fibers from the visceral organs) and the spinal trigeminal nucleus (the afferent somatic sensory fibers) (Patros et al., 2025; Fang et al., 2023; Hilz, 2022).

Mechanism of VNS

Vagus Nerve Stimulation is a medical treatment that involves an electrical device sending impulses through lead wires to an electrode cuff wrapped around the cervical bundle of the left vagus nerve. The pulse generator is implanted in the patient’s chest wall by a surgeon and activated after 2 weeks. It is then programmed by a neurologist or a psychiatrist, adjusting the parameters individually for each patient (Austelle, O’Leary, Thompson, et al., 2022). The exact mechanism of action of VNS is very complex. However, it is thought to involve the activation of both vagal afferent and efferent pathways, which transmit signals upward to the brain and downward to various internal organs (Fang et al., 2023).

Monoaminergic system

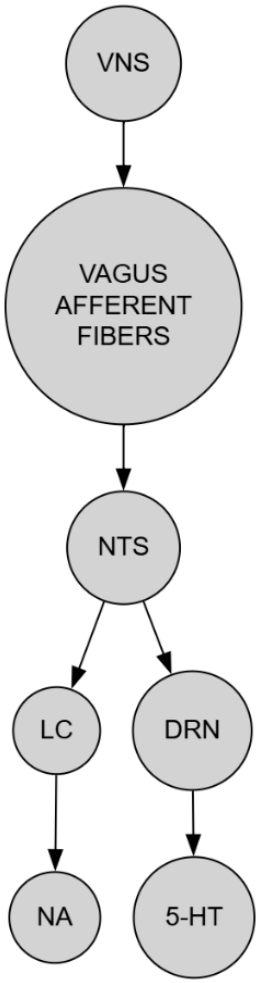

Fig. 1. *Vagus Nerve Stimmulation Leading to The Increased Hormonal Release [10,13]*
5-TH- serotonin; DRN- dorsal raphe nucleus ; LC- locus coeruleus; NA-noradrenaline; NTS- the nucleus of the solitary tract; VNS-vagus nerve stimulation.

The afferent fibers of the vagus nerve project to the nucleus of the solitary tract (NTS), which, in turn, sends secondary projections to the locus coeruleus (LC) and the dorsal raphe nucleus (DRN)—key centers of noradrenergic and serotonergic activity, respectively (Fang et al., 2023; Austelle et al., 2022) Both regions, along with their associated neurotransmitters, are believed to play major roles in the pathophysiology of depression (Austelle et al., 2022). Multiple studies have shown that VNS can enhance the release of noradrenaline (NA) in the LC and serotonin (5-HT) in the DRN Such modulation of neurotransmitter release may play a critical role in the antidepressant and anxiolytic actions of VNS (Wang et al., 2021a). Increased levels of NA and 5-HT have been shown to facilitate neuroplasticity, which may be particularly important for the long-term effects of VNS (Pigato et al., 2023).

Anti-inflammatory mechanisms

While inflammation serves as a protective response to external insults, excessive or chronic activation of inflammatory pathways has been implicated in the onset and progression of various neuropsychiatric disorders, including depression (Beurel, Toups, & Nemeroff, 2020; Wang et al., 2021b). In particular, stress-induced neuroinflammation—marked by the overproduction of inflammatory cytokines in the brain—has been recognized as a key contributor to depressive symptoms. Studies have demonstrated that the vagus nerve functions as a critical communication pathway between the central nervous system (CNS) and the immune system, and is playing a central role in the regulation of inflammatory responses (Wang et al., 2021b). A growing body of evidence suggests that the antidepressant effects of vagus nerve stimulation (VNS) may, in part, be mediated through the attenuation of systemic or local inflammation (Wang et al., 2021a).

Two primary mechanisms have been proposed to explain this anti-inflammatory effect: the vagal efferent and afferent pathways (Wang et al., 2021a).

Through the **efferent pathway**, VNS might activate parasympathetic vagal fibers projecting to the celiac ganglion in the upper abdomen. This, in turn, initiates a cascade involving T cells that migrate to the spleen and release of a neurotransmitter acetylcholine (ACh). ACh then binds to α7-nicotinic acetylcholine receptors (α7nAChRs) on macrophages resulting in the suppression of pro-inflammatory cytokine release, particularly tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) (Wang et al., 2021a; Fang et al., 2023). Vagal efferent fibers also suppress the cytokine production by gut macrophages through activation of α7 nicotinic acetylcholine receptors (α7nAChRs) (Fang et al., 2023). As a result, systemic inflammatory response is limited, contributing to the alleviation of depressive symptoms.

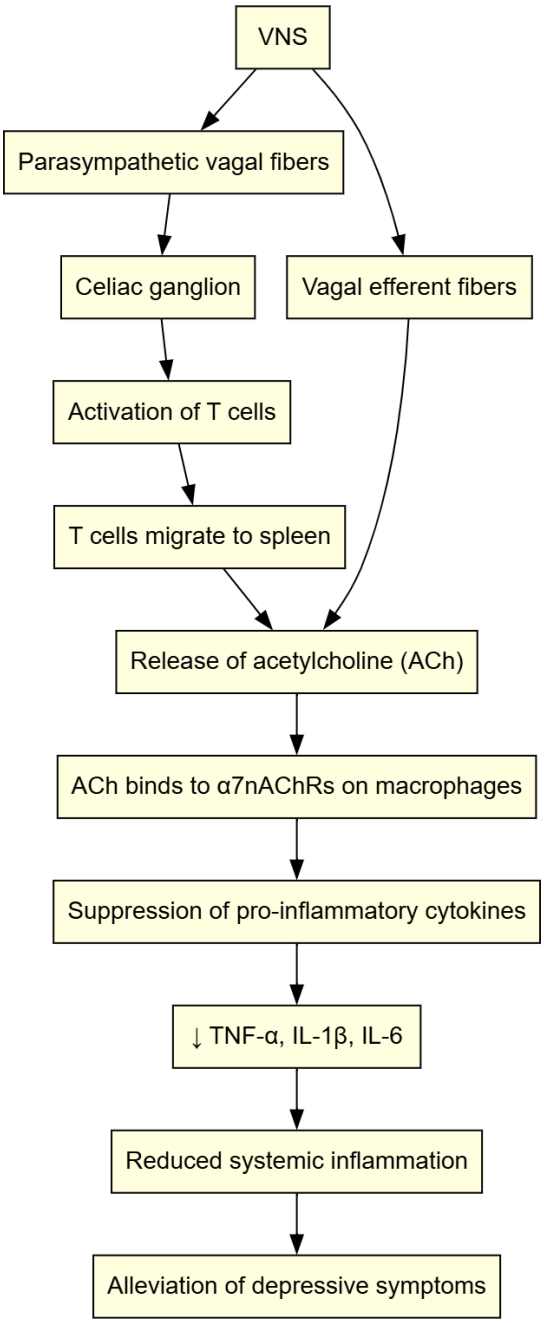

Fig. 2. *Anti-inflammatory mechanism-The efferent pathway [5, 10]*
ACh- Acetylocholine; α7nAChRs- α7-nicotinic acetylcholine receptors; TNF-α- tumor necrosis factor-alpha; VNS- vagus nerve stimulation

Through the **afferent pathway**, VNS may engage a parallel anti-inflammatory mechanism. Activation of afferent vagal fibers transmits signals to the nucleus of the solitary tract (NTS) at the base of the brainstem, which indirectly stimulates the basal forebrain cholinergic system, leading to increased release of ACh (Wang et al., 2021a; Wang et al., 2021b; Wang, J., Wang, Y., Chen, et al., 2025). Elevated ACh levels in the hippocampus bind to α7nAChRs on microglia—the brain's resident macrophages. Activation of these receptors shifts microglia toward a resting state and inhibits the release of pro-inflammatory cytokines. This reduces hippocampal (local) inflammation and alleviates depressive symptoms (Wang et al., 2021a; Wang et al., 2021b).

Additionally, VNS may activate the hypothalamic–pituitary–adrenal (HPA) axis via the afferent pathway. Stimulation of afferent vagal fibers leads to signal transmission to the NTS, which then projects to the hypothalamus, initiating the HPA axis cascade. This ultimately results in the secretion of glucocorticoids from the adrenal cortex (Fang et al., 2023). Glucocorticoids exert potent anti-inflammatory effects by modulating immune cell activity and suppressing pro-inflammatory cytokine production (Vandewalle, Luypaert, De Bosscher, & Libert, 2018).

Microbiota and neuroinflammation

Some studies suggest that VNS may exert its effects by modulating the microbiota–gut–brain axis. It is well established that abnormal changes in gut microbiota and their metabolites are closely associated with various brain disorders, including depression (Wang et al., 2021a). The microbiota can influence the brain through several pathways: via hormones produced in the intestines, such as serotonin (Wang et al., 2021a); through cytokines released by gut-associated lymphoid tissue (Faraji, Payami, Ebadpour, & Gorji, 2025); and via neural pathways connecting the gut and brain (Margolis, Cryan, & Mayer, 2021). Among these, the vagus nerve serves as the primary neuronal route linking the intestinal microbiota to the brain (Faraji et al., 2025).

This neuronal pathway can be described in more detail as follows: the gut microbiota produces a variety of metabolites that interact with the gastrointestinal microenvironment. Neuropods, specialized enteroendocrine cells, act as sensory transducers by detecting these signals and relaying them to afferent fibers of the vagus nerve, using glutamate as a neurotransmitter to transmit excitatory signals to vagal neurons (Margolis et al., 2021; Lespérance et al., 2024; Sun et al., 2024). The vagus nerve subsequently transmits these signals to NTS and further to higher brain regions, including the limbic system, thereby influencing emotional regulation and overall psychological well-being (Faraji et al., 2025; Margolis et al., 2021). Moreover, 5-HT3 receptors have been found on the vagus nerve, which indicates that 5-HT3 produced in the intestines could have an indirect impact on the central nervous system (Lespérance et al., 2024).

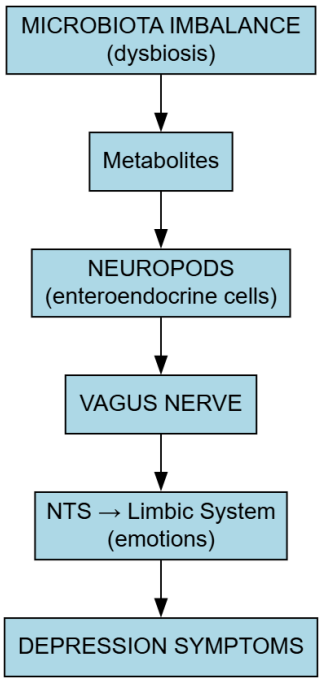

Fig. 3. *Gut-Brain-Axis [5,19,20]*
NTS- the nucleus of the solitary tract

Imbalances in the gut microbiota, such as dysbiosis, can disrupt communication between the gut and brain, contributing to the development of depression. VNS shows potential for modulating these complex systems and helping restore microbial balance. For example, a study by Yano et al. demonstrated that VNS promotes the growth of beneficial gut bacteria, including Lactobacillus and Bifidobacterium, which are known to support both gut and mental health (Faraji et al., 2025).

One of the mechanisms by which VNS modulates the microbiota–gut–brain axis is through the prevention of increased intestinal permeability (Wang et al., 2021a). Under pathological conditions characterized by elevated intestinal permeability, harmful metabolites and microbial-associated molecular patterns (MAMPs)—such as lipopolysaccharide (LPS)—can cross the epithelial barrier and enter the bloodstream, triggering systemic inflammation. Proinflammatory cytokines, including IL-1β, IL-6, TNF-α, and IFN-γ, may then cross the blood–brain barrier and induce neuroinflammatory responses within the central nervous system (Faraji et al., 2025), which contribute to the development of depressive symptoms. Thus, enhancing intestinal integrity through VNS could represent a promising therapeutic target for the treatment of depression.

Further research needed

However, some studies challenge the aforementioned anti-inflammatory mechanisms. In particular, one pilot study conducted by Lespérance and colleagues (Gerges et al., 2024) did not observe significant changes in the plasma levels of inflammatory proteins such as TNF-α, IL-6, or IFN-γ—cytokines previously implicated in VNS-mediated effects. Instead the study reported a significant reduction in chemokines CCL2, CCL13, and CCL17. These chemokines are associated with promoting immune cell migration. Thus VNS may be limiting the neuro-inflammation through reduced CCL2, CCL13, and CCL17 levels. Further research is necessary to determine the importance of specific inflammatory pathways involved in VNS-mediated immunomodulation.

Transcutaneous auricular vagus nerve stimulation

The use of traditional VNS in psychiatry is limited by side effects, surgical risks, and the high cost associated with the device and its implantation (Hilz, 2022). TaVNS offers a non-invasive alternative that addresses many of these limitations (Gianlorenco et al., 2022).

TaVNS is a method of modulating the brain physiology by stimulating the auricular branch of the vagus nerve (ABVN) (Go, Ju, Lee, Chae, & Song, 2022). The ABVN innervates the external auditory canal, and its fibers lie superficially enough to allow non-invasive stimulation (Hilz, 2022). Neuroanatomical studies have shown that the cymba conchae is exclusively innervated by the ABVN (Wang et al., 2021b), making it an optimal site for stimulation. During taVNS, electrodes are placed on the skin of the ear's concha, and a mild electrical current is delivered via wires connected to a small portable device (Thompson et al., 2021; Hilz, 2022). Unlike VNS, which provides continuous, automatic cycles of stimulation, taVNS is administered in set sessions (Tan, Qiao, Ma, Luo, Fang, & Yang, 2023). The parameters of taVNS are inconsistent and vary among many studies (Fang et al., 2023; Gianlorenco et al., 2022; Go et al., 2022; Li et al., 2022). Therefore, there is more research needed to indicate the optimum parameters.

While taVNS offers the significant advantage of being non-invasive, it is essential to assess its clinical effectiveness. A 2023 meta-analysis conducted by Tan C et al. confirmed that taVNS is indeed effective, demonstrating that patients receiving taVNS experienced significantly greater improvements in depressive symptoms compared to those receiving sham stimulation (Chen et al., 2023). Furthermore, the same meta-analysis reported that combining taVNS with antidepressant therapy (ATD) produced a more pronounced antidepressant effect than ATD alone. Supporting these findings, a comparative randomized trial by Shaoyuan Li et al. found that taVNS led to symptom improvement comparable to that achieved with citalopram, a commonly prescribed antidepressant (Wang, Q., Yang, & Liu, 2023). These results suggest that taVNS may serve as a viable alternative or adjunct to pharmacological treatments for depression.

Mechanism of taVNS

Although taVNS shows promise as an antidepressant intervention, its underlying mechanisms are not yet fully elucidated. Numerous studies have identified similarities in the physiological processes that underpin both invasive and non-invasive forms of vagus nerve stimulation (Patros et al., 2025; Hilz, 2022; Go et al., 2022). It is suggested ABVN activates afferent impulses that travel toward the NTS (Hilz, 2022; Go et al., 2022).Various functional imaging studies have shown that taVNS activates structures that are also activated by invasive VNS, including the locus coeruleus, dorsal raphe nucleus, and limbic regions (Hilz, 2022). This suggests that taVNS may have similar effects on the monoaminergic system, modulating both noradrenaline and serotonin release, and thus exerting antidepressant and anxiolytic effects.

taVNS immunomodulation

Numerous studies indicate that taVNS, similar to VNS, exerts antidepressant effects through the modulation of immune responses (Wang et al., 2021b; Wang et al., 2025a; Kaelberer, Rupprecht, Liu, Weng, & Bohórquez, 2020). Like VNS, taVNS is believed to engage the **afferent vagal pathway**. Studies have demonstrated that taVNS can activate the NTS (Wang et al., 2021a; Hilz, 2022) which in turn stimulates the basal forebrain cholinergic system to release ACh (Wang et al., 2021b). This ACh then binds to α7nAChRs in hippocampal region, mirroring the pathway activated by conventional VNS.

Furthermore, studies in rodent models suggest that taVNS increases the expression of α7nAChRs in the hippocampus, which may further enhance its anti-inflammatory and antidepressant effects (Wang et al., 2021b; Kaelberer et al., 2020).

Experimental studies in rodent models of depression have also demonstrated the critical role of α7nAChRs in mediating the anti-inflammatory and antidepressant effects of taVNS. Specifically, rats lacking functional α7nAChRs exhibit no significant improvement in behavioral or inflammatory outcomes following taVNS treatment (Wang et al., 2021b; Wang et al., 2025a; Kaelberer et al., 2020). These findings suggest that α7nAChR-dependent pathway may be fundamental in the antidepressant effects of taVNS in humans, although further clinical investigation is required to confirm this translational relevance.

4. Conclusions

Vagus Nerve Stimulation (VNS), both in its invasive and non-invasive forms, represents a promising and evolving therapeutic approach for the treatment of depression, particularly treatment-resistant cases. Rooted in its ability to modulate key neurobiological systems—including the monoaminergic neurotransmitter pathways, anti-inflammatory responses, and the microbiota–gut–brain axis—VNS influences multiple mechanisms implicated in the pathophysiology of depression. The development of transcutaneous auricular VNS (taVNS) offers a non-invasive alternative that mitigates many limitations associated with traditional VNS, including surgical risks and high costs, while demonstrating comparable efficacy in improving depressive symptoms.

Given the growing body of clinical and preclinical data, VNS and taVNS stand as valuable adjunct or alternative therapies for depression, warranting continued exploration in larger, controlled trials. Future investigations should aim to deepen the understanding of their mechanistic pathways, refine patient selection, and enhance therapeutic outcomes, ultimately expanding the arsenal of effective interventions against major depressive disorder.

Author's contribution:

Conceptualization: Julia Guzowska; Weronika Suchcicka; Patrycja Rzeźnik; Barbara Wołoszyn; Małgorzata Zach; Julia Stępień; Aleksandra Borowy; Maciej Sobczak; Weronika Stachera; Aleksandra Chajnowska

Methodology: Weronika Suchcicka; Patrycja Rzeźnik; Barbara Wołoszyn; Małgorzata Zach; Julia Stępień; Aleksandra Borowy; Maciej Sobczak; Weronika Stachera; Aleksandra Chajnowska; Julia Guzowska

Software: Patrycja Rzeźnik; Barbara Wołoszyn; Małgorzata Zach; Julia Stępień; Aleksandra Borowy; Maciej Sobczak; Weronika Stachera; Aleksandra Chajnowska; Julia Guzowska; Weronika Suchcicka;

Check: Barbara Wołoszyn; Małgorzata Zach; Julia Stępień; Aleksandra Borowy; Maciej Sobczak; Weronika Stachera; Aleksandra Chajnowska; Julia Guzowska; Weronika Suchcicka; Patrycja Rzeźnik;

Formal analysis: Małgorzata Zach; Julia Stępień; Aleksandra Borowy; Maciej Sobczak; Weronika Stachera; Aleksandra Chajnowska; Julia Guzowska; Weronika Suchcicka; Patrycja Rzeźnik; Barbara Wołoszyn;

Investigation: Julia Stępień; Aleksandra Borowy; Maciej Sobczak; Weronika Stachera; Aleksandra Chajnowska; Julia Guzowska; Weronika Suchcicka; Patrycja Rzeźnik; Barbara Wołoszyn; Małgorzata Zach;

Resources Aleksandra Borowy; Maciej Sobczak; Weronika Stachera; Aleksandra Chajnowska; **:** Julia Guzowska; Weronika Suchcicka; Patrycja Rzeźnik; Barbara Wołoszyn; Małgorzata Zach; Julia Stępień;

Data curation: Maciej Sobczak; Weronika Stachera; Aleksandra Chajnowska; Julia Guzowska; Weronika Suchcicka; Patrycja Rzeźnik; Barbara Wołoszyn; Małgorzata Zach; Julia Stępień; Aleksandra Borowy;

Writing - rough preparation: Julia Guzowska; Weronika Suchcicka; Patrycja Rzeźnik; Barbara Wołoszyn; Małgorzata Zach; Julia Stępień; Aleksandra Borowy; Maciej Sobczak; Weronika Stachera; Aleksandra Chajnowska

Writing - review and editing: Weronika Stachera; Aleksandra Chajnowska; Julia Guzowska; Weronika Suchcicka; Patrycja Rzeźnik; Barbara Wołoszyn; Małgorzata Zach; Julia Stępień; Aleksandra Borowy; Maciej Sobczak;

Supervision: Weronika Stachera; Aleksandra Chajnowska; Julia Guzowska; Weronika Suchcicka; Patrycja Rzeźnik; Barbara Wołoszyn; Małgorzata Zach; Julia Stępień; Aleksandra Borowy; Maciej Sobczak

Project administration: Aleksandra Chajnowska; Julia Guzowska; Weronika Suchcicka; Patrycja Rzeźnik; Barbara Wołoszyn; Małgorzata Zach; Julia Stępień; Aleksandra Borowy; Maciej Sobczak; Weronika Stachera;

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This research received no external founding.
Institutional Review Board Statement: Not applicable
Informed Consent Statement: Not applicable
Data Availability Statement: Not applicable
Conflict of Interest Statement: The authors declare no conflict of interests

Declaration on the Use of AI

In preparing this manuscript, the authors used ChatGPT for language improvement and enhancing readability. Following the use of this tool, all content was reviewed and edited by the authors, who take full responsibility for the accuracy and integrity of the final version.

REFERENCES

1. Andalib, S., Divani, A. A., Ayata, C., Baig, S., Arsava, E. M., Topcuoglu, M. A., Cáceres, E. L., Parikh, V., Desai, M. J., Majid, A., Girolami, S., & Di Napoli, M. (2023). Vagus nerve stimulation in ischemic stroke. *Current Neurology and Neuroscience Reports, 23*(12), 947–962. https://doi.org/10.1007/s11910-023-01323-w
2. Attenello, F., Amar, A. P., Liu, C., & Apuzzo, M. L. (2015). Theoretical basis of vagus nerve stimulation. *Progress in Neurological Surgery, 29,* 20–28. https://doi.org/10.1159/000434652
3. Austelle, C. W., Cox, S. S., Wills, K. E., & Badran, B. W. (2024). Vagus nerve stimulation (VNS): Recent advances and future directions. *Clinical Autonomic Research, 34*(6), 529–547. https://doi.org/10.1007/s10286-024-01065-w
4. Austelle, C. W., O'Leary, G. H., Thompson, S., Gruber, E., Kahn, A., Manett, A. J., Short, B., & Badran, B. W. (2022). A comprehensive review of vagus nerve stimulation for depression. *Neuromodulation, 25*(3), 309–315. https://doi.org/10.1111/ner.13528
5. Baquiran, M., & Bordoni, B. (2023). Anatomy, head and neck: Anterior vagus nerve. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK549814/
6. Chen, Y., Zhang, Y., Wang, J., Li, S., Wang, Y., Zhang, Z., Zhang, J., Xin, C., Wang, Y., & Rong, P. (2023). Anti-neuroinflammation effects of transcutaneous auricular vagus nerve stimulation against depression-like behaviors via hypothalamic α7nAchR/JAK2/STAT3/NF-κB pathway in rats exposed to chronic unpredictable mild stress. *CNS Neuroscience & Therapeutics, 29*(9), 2634–2644. https://doi.org/10.1111/cns.14207
7. Fang, Y. T., Lin, Y. T., Tseng, W. L., Tseng, P., Hua, G. L., Chao, Y. J., & Wu, Y. J. (2023). Neuroimmunomodulation of vagus nerve stimulation and the therapeutic implications. *Frontiers in Aging Neuroscience, 15,* 1173987. https://doi.org/10.3389/fnagi.2023.1173987
8. Faraji, N., Payami, B., Ebadpour, N., & Gorji, A. (2025). Vagus nerve stimulation and gut microbiota interactions: A novel therapeutic avenue for neuropsychiatric disorders. *Neuroscience & Biobehavioral Reviews, 169,* 105990. https://doi.org/10.1016/j.neubiorev.2024.105990
9. Gerges, A. N. H., Williams, E. E. R., Hillier, S., Uy, J., Hamilton, T., Chamberlain, S., & Hordacre, B. (2024). Clinical application of transcutaneous auricular vagus nerve stimulation: A scoping review. *Disability and Rehabilitation, 46*(24), 5730–5760. https://doi.org/10.1080/09638288.2024.2313123
10. Gianlorenco, A. C. L., de Melo, P. S., Marduy, A., Kim, A. Y., Kim, C. K., Choi, H., Song, J. J., & Fregni, F. (2022). Electroencephalographic patterns in taVNS: A systematic review. *Biomedicines, 10*(9), 2208. https://doi.org/10.3390/biomedicines10092208
11. Go, Y. Y., Ju, W. M., Lee, C. M., Chae, S. W., & Song, J. J. (2022). Different transcutaneous auricular vagus nerve stimulation parameters modulate the anti-inflammatory effects on lipopolysaccharide-induced acute inflammation in mice. *Biomedicines, 10*(2), 247. https://doi.org/10.3390/biomedicines10020247
12. Hilz, M. J. (2022). Transcutaneous vagus nerve stimulation: A brief introduction and overview. *Autonomic Neuroscience, 243,* 103038. https://doi.org/10.1016/j.autneu.2022.103038

13. Kaelberer, M. M., Rupprecht, L. E., Liu, W. W., Weng, P., & Bohórquez, D. V. (2020). Neuropod cells: The emerging biology of gut–brain sensory transduction. *Annual Review of Neuroscience, 43,* 337–353. https://doi.org/10.1146/annurev-neuro-091619-022657
14. Kenny, B. J., & Bordoni, B. (2022). Neuroanatomy, cranial nerve 10 (vagus nerve). In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK549814/
15. Kraus, C., Quach, D., Sholtes, D. M., Kavakbasi, E., De Zwaef, R., Dibué, M., Zajecka, J., & Baune, B. T. (2022). Setting up a successful vagus nerve stimulation service for patients with difficult-to-treat depression. *Neuromodulation, 25*(3), 316–326. https://doi.org/10.1016/j.neurom.2021.12.010
16. Lespérance, P., Desbeaumes Jodoin, V., Drouin, D., Racicot, F., Miron, J. P., Longpré-Poirier, C., Fournier-Gosselin, M. P., Thebault, P., Lapointe, R., Arbour, N., & Cailhier, J. F. (2024). Vagus nerve stimulation modulates inflammation in treatment-resistant depression patients: A pilot study. *International Journal of Molecular Sciences, 25*(5), 2679. https://doi.org/10.3390/ijms25052679
17. Li, S., Rong, P., Wang, Y., Jin, G., Hou, X., Li, S., Xiao, X., Zhou, W., Wu, Y., Liu, Y., Zhang, Y., Zhao, B., Huang, Y., Cao, J., Chen, H., Hodges, S., Vangel, M., & Kong, J. (2022). Comparative effectiveness of transcutaneous auricular vagus nerve stimulation vs citalopram for major depressive disorder: A randomized trial. *Neuromodulation, 25*(3), 450–460. https://doi.org/10.1016/j.neurom.2021.10.021
18. Margolis, K. G., Cryan, J. F., & Mayer, E. A. (2021). The microbiota–gut–brain axis: From motility to mood. *Gastroenterology, 160*(5), 1486–1501. https://doi.org/10.1053/j.gastro.2020.10.066
19. Patros, M., Sivathamboo, S., Simpson, H. D., O'Brien, T. J., & Macefield, V. G. (2025). The physiology, anatomy and stimulation of the vagus nerve in epilepsy. *The Journal of Physiology, 603*(8), 2201–2217. https://doi.org/10.1113/JP287164
20. Pigato, G., Rosson, S., Bresolin, N., Toffanin, T., Sambataro, F., Olivo, D., Perini, G., Causin, F., Denaro, L., Landi, A., & D'Avella, D. (2023). Vagus nerve stimulation in treatment-resistant depression: A case series of long-term follow-up. *Journal of ECT, 39*(1), 23–27. https://doi.org/10.1097/YCT.0000000000000869
21. Sun, J., Sun, K., Chen, L., Li, X., Xu, K., Guo, C., Ma, Y., Cao, J., Zhang, G., Hong, Y., Wang, Z., Gao, S., Luo, Y., Chen, Q., Ye, W., Yu, X., Xiao, X., Rong, P., Yu, C., & Fang, J. (2024). A predictive study of the efficacy of transcutaneous auricular vagus nerve stimulation in the treatment of major depressive disorder: An fMRI-based machine learning analysis. *Asian Journal of Psychiatry, 98,* 104079. https://doi.org/10.1016/j.ajp.2024.104079
22. Tan, C., Qiao, M., Ma, Y., Luo, Y., Fang, J., & Yang, Y. (2023). The efficacy and safety of transcutaneous auricular vagus nerve stimulation in the treatment of depressive disorder: A systematic review and meta-analysis of randomized controlled trials. *Journal of Affective Disorders, 337,* 37–49. https://doi.org/10.1016/j.jad.2023.05.048
23. Thompson, S. L., O'Leary, G. H., Austelle, C. W., Gruber, E., Kahn, A. T., Manett, A. J., Short, B., & Badran, B. W. (2021). A review of parameter settings for invasive and non-invasive vagus nerve stimulation (VNS) applied in neurological and psychiatric disorders. *Frontiers in Neuroscience, 15,* 709436. https://doi.org/10.3389/fnins.2021.709436
24. Vandewalle, J., Luypaert, A., De Bosscher, K., & Libert, C. (2018). Therapeutic mechanisms of glucocorticoids. *Trends in Endocrinology & Metabolism, 29*(1), 42–54. https://doi.org/10.1016/j.tem.2017.10.010
25. Wang, J., Wang, Y., Chen, Y., Zhang, J., Zhang, Y., Li, S., Zhu, H., Song, X., Hou, L., Wang, L., Wang, Y., Zhang, Z., & Rong, P. (2025). Transcutaneous auricular vagus stimulation attenuates LPS-induced depression-like behavior by regulating central α7nAChR/JAK2 signaling. *Molecular Neurobiology, 62*(3), 3011–3023. https://doi.org/10.1007/s12035-024-04438-4
26. Wang, J. Y., Zhang, Y., Chen, Y., Wang, Y., Li, S. Y., Wang, Y. F., Zhang, Z. X., Zhang, J., & Rong, P. (2021). Mechanisms underlying antidepressant effect of transcutaneous auricular vagus nerve stimulation on CUMS model rats based on hippocampal α7nAchR/NF-κB signal pathway. *Journal of Neuroinflammation, 18*(1), 291. https://doi.org/10.1186/s12974-021-02341-6
27. Wang, Q., Yang, Q., & Liu, X. (2023). The microbiota–gut–brain axis and neurodevelopmental disorders. *Protein & Cell, 14*(10), 762–775. https://doi.org/10.1093/procel/pwad026
28. Wang, Y., Zhan, G., Cai, Z., Jiao, B., Zhao, Y., Li, S., & Luo, A. (2021). Vagus nerve stimulation in brain diseases: Therapeutic applications and biological mechanisms. *Neuroscience & Biobehavioral Reviews, 127,* 37–53. https://doi.org/10.1016/j.neubiorev.2021.04.018