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Vagus Nerve Stimulation in Neurology and Beyond: A Comprehensive Review of Clinical Use, Mechanisms, Innovations and Future Directions

1. **Michał Janiszewski [MJ]**
   ORCID: https://orcid.org/0009-0007-8932-3808
   1michal.janiszewski@gmail.com
   Mazovian "Bródnowski" Hospital
   Ludwika Kondratowicza 8, 03-242 Warsaw, Poland

2. **Marcin Komorowski [MK]**
   ORCID: https://orcid.org/0009-0009-1423-7176
   mkomorowski16@gmail.com
   Międzylesie Specialist Hospital
   Bursztynowa 2, 04-749 Warsaw, Poland

3. **Joanna Piecek [JP]**
   ORCID: https://orcid.org/0009-0003-6729-2386
   joasiapiecek@gmail.com
   Medical University of Warsaw
   Żwirki i Wigury 61, 02-091 Warsaw, Poland

4. **Marta Omiecińska [MO]**
ORCID: https://orcid.org/0009-0002-3134-8141
martaomiecinska@gmail.com
Międzylesie Specialist Hospital
Bursztynowa 2, 04-749 Warsaw, Poland

5. **Natalia Surosz [NS]**
ORCID: https://orcid.org/0009-0005-1939-151X
natalia.surosz@gmail.com
Międzylesie Specialist Hospital
Bursztynowa 2, 04-749 Warsaw, Poland

6. **Aleksandra Graczyk [AG]**
ORCID: https://orcid.org/0009-0006-3505-1416
graczyk.aaleksandra@gmail.com
Medical University of Warsaw
Żwirki i Wigury 61, 02-091 Warsaw, Poland

7. **Michał Grochowalski [MG]**
ORCID: https://orcid.org/0009-0005-0293-9411
michalgrochlag@gmail.com
Nicolaus Copernicus Memorial Hospital
93-513 Lodz, Poland

8. **Jakub Szydło [JS]**
ORCID: https://orcid.org/0009-0009-1092-2571
jakubszydlorekrutacja@interia.pl
Independent Public Complex of Outpatient Health Care Centers Warsaw
Żoliborz-Bielany, Karola Szajnochy 8, 01-637 Warsaw, Poland

9. **Dominika Ziętara [DZ]**
ORCID: https://orcid.org/0009-0000-2535-7995
dominika.zietara@vp.pl
Międzylesie Specialist Hospital, Bursztynowa 2, 04-749 Warsaw, Poland

10. Kacper Kmieć [KK]

ORCID: https://orcid.org/0009-0000-8076-2387

kmiec.k4cper@gmail.com

Międzylesie Specialist Hospital, Bursztynowa 2, 04-749 Warsaw, Poland

ABSTRACT

Background. Vagus nerve stimulation (VNS) has evolved from a treatment for drug-resistant epilepsy (DRE) into a broader neuromodulatory platform with expanding applications in neurology, psychiatry, immunology, and cardiology. Technological advances, particularly in non-invasive and adaptive modalities, have renewed interest in its therapeutic potential.

Aim. To provide a comprehensive review of the clinical applications, mechanisms of action, safety profile, and emerging technological innovations in VNS, with emphasis on non-invasive techniques, adaptive stimulation, candidate biomarkers, and associated ethical considerations.

Material and Methods. This narrative review synthesizes findings from peer-reviewed studies, clinical trials, and experimental reports identified through targeted searches in PubMed, Google Scholar, and related databases.

Results. VNS demonstrates consistent efficacy in reducing seizure frequency in epilepsy and improving outcomes in treatment-resistant depression (TRD), inflammatory conditions, and cardiovascular disorders. Mechanistically, it modulates brainstem–cortical circuits, autonomic tone, and neuroimmune signaling pathways. Side effects are typically mild and transient. Non-invasive and closed-loop systems show promise in enhancing individualization and tolerability, although challenges remain in terms of standardization, long-term data, and equitable access.

Conclusions. VNS represents a safe, increasingly personalized intervention with broad therapeutic scope. Future research should prioritize biomarker validation, optimization of stimulation paradigms, and integration with artificial intelligence (AI) and digital health tools, ensuring ethical and scalable implementation across diverse clinical populations.

Keywords: Vagus Nerve Stimulation, Drug-Resistant Epilepsy, Biomarkers, Neuroimmunomodulation, Closed-Loop Neuromodulation, Bioelectronic Medicine

INTRODUCTION

1) Background and Historical Perspective of VNS

The conceptual origins of VNS date back to the late 1800s, when Dr. James Corning hypothesised that electrically stimulating the carotid sheath—including the vagus nerve—might influence cerebral perfusion and mitigate epileptic activity [1,2]. Although these early explorations were constrained by technological limitations and yielded minimal clinical success, the foundational idea resurfaced in the 1980s, bolstered by animal model research that demonstrated significant seizure-suppressing effects of VNS [3,4]. The inaugural human implantation was performed in 1988, and by 1997, the United States Food and Drug Administration (FDA) had approved VNS devices for DRE [5,6]. Since that time, the therapeutic scope of VNS has broadened, encompassing conditions such as treatment-resistant depression, cluster headaches, migraines, and certain inflammatory diseases [7–9].

2) Physiological Basis and Mechanisms of Action

The vagus nerve serves as a central conduit in the parasympathetic nervous system, innervating numerous visceral organs and orchestrating key autonomic, immune, and neurochemical processes [9,10]. VNS exerts its therapeutic influence partly through activation of the cholinergic anti-inflammatory pathway (CAP), wherein acetylcholine released by efferent vagal fibres binds to α7 nicotinic acetylcholine receptors (α7nAChRs) on immune cells. This interaction downregulates the expression of pro-inflammatory cytokines—such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β)—via the Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) pathway [11,12]. Neuroimaging studies have shown that VNS modulates activity in several brain regions, including the nucleus tractus solitarius (NTS), hippocampus, amygdala, and prefrontal cortex—areas critically involved in mood regulation, cognitive function, and autonomic balance [13]. Furthermore, VNS has been implicated in enhancing neural plasticity and conferring neuroprotective effects, thereby underlining its utility in both neurological and psychiatric contexts.

3) Rationale and Objectives of the Review

As clinical indications for VNS continue to proliferate and novel non-invasive modalities gain traction, there is a growing need for an integrative review that captures the state of current research. This article aims to delineate the physiological underpinnings of VNS, compare invasive and non-invasive delivery systems, and evaluate stimulation parameters that influence clinical efficacy. By synthesizing mechanistic insights with recent technological advances, we seek to inform both future research and clinical best practices.

CHAPTER 1: Technical Aspects and Modalities of VNS

1) Invasive vs. Non-invasive Approaches:

VNS represents a robust neuromodulatory intervention with diverse clinical applications. Historically, VNS has relied predominantly on invasive approaches (iVNS-invasive vagus nerve stimulation), which require surgical implantation. However, significant progress in both biomedical engineering and clinical research has enabled the development of non-invasive vagus nerve stimulation (nVNS) devices [14]. Both iVNS and nVNS modalities have shown efficacy in the treatment of various conditions, including epilepsy, major depressive disorder, and motor impairment following stroke [15].

The iVNS technique involves surgically placing electrodes around the left cervical vagus nerve, generally under general or local anaesthesia. The pulse generator is implanted subcutaneously, typically in the thoracic region, to facilitate continuous stimulation. While this method provides direct access to vagal fibres, it also introduces procedural risks such as bradycardia, vocal cord paresis, local infections, and tracheal hematomas [15].

Non-invasive approaches, by contrast, employ transcutaneous stimulation and are categorised into two primary techniques: transcutaneous auricular VNS (taVNS) and transcutaneous cervical VNS (tcVNS). TaVNS targets the auricular branch of the vagus nerve (ABVN), with stimulation commonly administered to regions such as the cymba conchae and antihelix [14]. Yakunina et al. identified the cymba conchae as an optimal site for vagal engagement [16]. TcVNS, on the other hand, delivers electrical impulses through the skin overlying the cervical vagus nerve using handheld stimulators. Functional magnetic resonance

imaging (fMRI) data suggest that both taVNS and tcVNS can produce neuromodulatory effects comparable to those achieved via invasive methods [17,18].

A notable innovation in this domain is closed-loop taVNS (CL-taVNS), formally introduced in 2020. This method integrates biofeedback systems to dynamically modulate stimulation. Subtypes include motor-activated auricular VNS (MAAVNS), which utilises electromyographic feedback to time stimulation with physical activity [19], and respiratory-gated auricular vagal afferent nerve stimulation (RAVANS) [19], which leverages the transient suppression of vagal tone during inhalation Future directions may involve EEG-, ECG-, or humoral signal-based systems—potentially enhanced by AI-driven algorithms—to further tailor stimulation protocols and improve therapeutic precision.

While taVNS is lauded for its non-invasive nature and user-friendliness, its mechanistic pathways remain partially elucidated. Emerging evidence suggests that ABVN stimulation may influence central autonomic structures such as the NTS and locus coeruleus, contributing to modulation of autonomic tone and inflammatory responses [16–18].

2) Devices and Technological Developments:

Between 1988 and 2020, VNS technology experienced notable milestones, from the first human implantation [20] to multiple FDA approvals. These include the 1997 endorsement for epilepsy and the 2005 approval for treatment-resistant depression. Successive generations of implantable devices demonstrate evolving capabilities in terms of programmability, magnetic resonance imaging (MRI) compatibility, and paediatric use. The SenTiva Duo™ (M1000-D), introduced by 2020, further expanded clinical applicability with enhanced imaging support. Despite advancements and widespread adoption, the clinical debate continues regarding the comparative efficacy, safety, and underlying mechanisms of implantable versus non-invasive VNS technologies [21].

Advanced implantable systems now feature programmable stimulators with improved battery life and refined current delivery options. Some experimental devices incorporate kilohertz-frequency blocking electrodes to selectively inhibit undesirable nerve signals while preserving therapeutic efficacy—findings supported by preclinical rodent studies [22].

TaVNS devices generally employ clip-on electrodes applied to the outer ear and are conducive to outpatient administration. Vagal activation is often confirmed by monitoring

physiological biomarkers such as heart rate variability, a surrogate marker for parasympathetic engagement [13,23,24].

3) Stimulation Parameters and Protocols:

Therapeutic outcomes in VNS are highly dependent on the fine-tuning of stimulation parameters—namely, pulse width, frequency, and current intensity. Preclinical studies have identified a non-linear, inverted U-shaped dose-response relationship, with mid-range intensities (~0.8 mA) promoting optimal cortical plasticity, whereas sub- or supra-optimal intensities yield diminished results [25]. Standard clinical settings for implantable VNS typically utilise currents between 0.25 and 3.75 mA, pulse durations of 100–500 μs, and frequencies in the range of 20–30 Hz. For non-invasive applications, parameters vary according to indication. For instance, taVNS protocols targeting depressive symptoms often prescribe one to two 15-minute sessions daily, whereas cluster headache regimens may involve both prophylactic and acute treatment cycles [26–28]. The refinement of these protocols remains a focal point of ongoing research, aimed at balancing efficacy with safety.

CHAPTER 2: Established Clinical Indications

1) VNS in Epilepsy:

VNS is an FDA-approved neuromodulatory treatment designed for patients with pharmacoresistant focal epilepsy. Since its authorization in 1997 for adults and subsequent extension to children aged 4 and above in 2017, VNS has gained prominence as a therapeutic choice for individuals ineligible for resective surgery or those with unsuccessful surgical outcomes [29]. Unlike resective interventions, VNS is a minimally invasive, non-destructive, and reversible procedure that delivers chronic stimulation to the left cervical vagus nerve to modulate seizure activity [30]. Its anticonvulsant mechanisms are believed to involve the disruption of pathological neural synchrony, alterations in neurotransmitter dynamics, especially norepinephrine and gamma-aminobutyric acid (GABA), and reduction in cortical excitability. These therapeutic effects typically emerge over time, with maximal improvement often observed after several months of continued stimulation [31].

Evidence from clinical and observational research indicates that approximately 40–60% of recipients experience a reduction in seizure frequency of at least 50%. VNS has also been

associated with reduced seizure intensity and duration, as well as shortened postictal periods, contributing to enhanced daily functioning and quality of life. Although complete seizure remission is uncommon, VNS often augments the effectiveness of pharmacological regimens [32,33].

Although originally intended for focal epilepsy, VNS has demonstrated efficacy regardless of whether the epilepsy is focal or generalized. Increasing awareness of focal features within generalized epilepsy, such as distinct seizure manifestations and localized EEG abnormalities, suggests that VNS may be underused in generalized epilepsy cases [34]. Moreover, patients with multiple seizure types, particularly those involving drop attacks or tonic-clonic episodes, may benefit substantially from VNS, especially when drug therapy proves insufficient [31,35].

Among children, VNS has shown promise, notably in those diagnosed with developmental and epileptic encephalopathies, Lennox-Gastaut syndrome, or post-surgical refractory epilepsy. Favorable outcomes have been observed even in pediatric patients following unsuccessful surgical interventions [36]. Some children exhibit behavioral benefits, such as diminished irritability, enhanced concentration, and improved sleep, even in cases where seizure reduction is modest [37]. In select scenarios, combining VNS with ketogenic dietary therapy has yielded synergistic effects in decreasing seizure burden [38].

Technological improvements in VNS systems have enhanced their therapeutic capabilities. Devices like AspireSR® and SenTiva® now feature closed-loop systems capable of detecting seizure-associated tachycardia and delivering responsive stimulation accordingly [21]. This functionality has been linked with better seizure control, reduced caregiver burden, and greater ease of use [21,39]. These devices also enable more refined and patient-specific adjustments of stimulation parameters, improving the balance between efficacy and tolerability [39].

Surgically, VNS implantation is generally considered safe and well tolerated. The procedure entails implanting a pulse generator subcutaneously in the chest and wrapping the lead around the left vagus nerve in the neck, typically on the left side to avoid right-sided cardiac efferents [30]. Common but mild stimulation-related side effects include hoarseness, voice changes, throat discomfort, and dyspnea, which often diminish with dose modification or time. Severe complications such as infection, lead failure, or vocal cord paralysis are rare. In pediatric

patients, device revisions may occasionally be required due to anatomical growth or hardware-related issues [40].

Despite its documented benefits, VNS remains underutilized. Contributing factors include delayed referrals, limited regional access, and misconceptions about its applicability. Although not a curative measure, VNS offers a durable, low-risk adjunctive treatment for reducing seizures, particularly when other therapeutic options are exhausted [41].

2) VNS in Treatment-Resistant Depression:

TRD continues to pose a significant therapeutic challenge in psychiatry, affecting up to 30% of individuals who do not respond sufficiently to multiple antidepressant trials. VNS has emerged as a neuromodulatory intervention for patients with persistent and refractory major depressive disorder (MDD). After encouraging initial findings, the FDA authorized its use in 2005 as an adjunctive treatment for adults with unipolar or bipolar depression who had not responded to at least four adequate antidepressant strategies [42].

Long-term application of VNS has been associated with increased activation of serotonergic and noradrenergic pathways, upregulation of brain-derived neurotrophic factor (BDNF), stabilization of hypothalamic-pituitary-adrenal (HPA) axis functioning, and enhanced neural plasticity [43,44]. Neuroimaging investigations have shown perfusion changes in both cortical and subcortical areas following stimulation, with notable involvement of the orbitofrontal and insular cortices, regions frequently implicated in MDD pathology [16,45].

The therapeutic value of implanted VNS for TRD has been supported by multiple studies. For instance, one randomized controlled trial demonstrated a positive correlation between electrical dose and treatment response, with higher stimulation levels associated with greater clinical improvement over time [46]. A meta-analysis aggregating results from several open-label studies reported that VNS leads to meaningful symptom reduction in approximately 40–50% of patients, with remission rates of 20–30%, which are comparable to or exceed typical outcomes from pharmacological approaches in similar populations [47]. In addition to symptom reduction, VNS has been linked to functional benefits such as enhanced social functioning, increased occupational engagement, improved energy, and reduced suicidal ideation [48].

TaVNS represents a promising, non-invasive alternative for patients who may not qualify for or prefer to avoid surgical implantation. TaVNS delivers stimulation to the ABVN,

particularly at the tragus and cymba conchae, areas with dense vagal innervation [49,50]. Both anatomical and imaging-based studies validate taVNS as a central neuromodulatory method. FMRI and positron emission tomography (PET) scans have demonstrated that taVNS activates brain structures similar to those influenced by invasive VNS, including the insular cortex, prefrontal regions, and brainstem nuclei [45]. Additional confirmation of physiological efficacy comes from HRV and brainstem response analyses conducted during stimulation [23].

Clinical evidence supporting the use of taVNS in depressive disorders is steadily growing. One randomized controlled trial showed notable reductions in depressive symptoms among individuals with post-stroke depression, suggesting that taVNS may exert both mood-enhancing and neuroprotective effects [51]. Prior pilot studies and systematic reviews have also indicated that taVNS improves scores on depression rating scales such as the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI), while maintaining excellent tolerability [52,53].

Nonetheless, the current body of taVNS research is predominantly composed of small-scale or open-label trials, limiting generalizability. More robust data, including head-to-head studies comparing different VNS approaches and large, double-blind randomized controlled trials, are essential for determining relative efficacy and shaping clinical guidelines.

3) VNS in Migraine Management:

VNS has garnered increasing interest as a non-invasive neuromodulatory intervention for the treatment of primary headache syndromes, most notably migraine and cluster headache. Although iVNS was initially designed for epilepsy management, the development of nVNS, particularly transcutaneous cervical stimulation using handheld devices like gammaCore®, has expanded its neurological indications, including both abortive and prophylactic therapy for migraine attacks [54].

The therapeutic rationale for VNS in migraine is grounded in its effects on various pathophysiological processes. These include suppression of cortical spreading depression, modulation of trigeminovascular nociceptive transmission, activation of the cholinergic anti-inflammatory pathway, and regulation of autonomic nervous system balance. Functional neuroimaging data suggest that nVNS influences neural circuits implicated in migraine, such as the thalamus, brainstem, and limbic structures [54,55].

Early support for nVNS in acute migraine came from an open-label exploratory study, where 22% of participants experienced complete pain relief within two hours, and 46% reported at least a 50% reduction in pain intensity [55]. These preliminary findings were substantiated by the PRESTO trial, a randomized controlled study involving episodic migraine sufferers. The trial demonstrated significant improvements in outcomes such as pain freedom at 30 and 60 minutes, resolution of the most bothersome symptom, and reduced need for rescue medications within two hours in the nVNS group compared to sham stimulation [56].

The utility of nVNS as a preventive migraine treatment has also been investigated. In the PREMIUM trial, the efficacy of nVNS was evaluated over a 12-week period in patients with episodic migraine experiencing 5–12 headache days per month. Although the primary endpoint, reduction in monthly migraine days, did not achieve statistical significance across the entire study population, a subgroup analysis showed significant benefit among individuals with a higher frequency of attacks (≥8 migraine days/month), indicating that nVNS may be particularly helpful in this subset [57].

Beyond migraine, nVNS has been the subject of extensive research in cluster headache, a condition sharing some overlapping mechanisms with migraine. Results from two major randomized controlled trials, ACT1 and ACT2, demonstrated that nVNS significantly improved pain-free rates within 15 minutes in patients with episodic cluster headache and exhibited favorable trends in those with the chronic form [58,59].

In conclusion, nVNS represents a promising and generally well-tolerated therapeutic option for both acute relief and prevention in patients with episodic and chronic migraine. While ongoing research continues to refine its precise clinical role, the growing body of evidence supports its inclusion in comprehensive headache management strategies, particularly for patients with refractory symptoms or contraindications to pharmacological treatments.

4) VNS in Post-Stroke Recovery:

Stroke remains a major contributor to long-term disability globally, with ischemic strokes accounting for the vast majority of cases. Given the limitations of traditional rehabilitation in restoring motor function, VNS has gained attention as a novel strategy aimed at enhancing neuroplasticity and facilitating motor recovery after stroke [60].

A pivotal advancement in this field came from the VNS-REHAB trial - a multicenter, double-blind, randomized controlled study, which assessed the effects of implanted VNS combined with upper-limb therapy in individuals with moderate-to-severe upper extremity impairment following ischemic stroke. Patients treated with VNS achieved significantly greater improvements in arm function, as indicated by gains on the Fugl-Meyer Assessment for the Upper Extremity (FMA-UE), with a mean difference of 5.8 points compared to controls. Furthermore, a greater proportion of participants in the VNS group met the threshold for clinically meaningful recovery [61]. These therapeutic effects persisted at the 90-day follow-up, and the intervention was well tolerated, with no serious adverse events linked to stimulation.

Interest has also been growing in taVNS as a potentially safer and more accessible alternative to surgical implantation. Preliminary studies have shown that pairing taVNS with repetitive task training can enhance both motor and sensory recovery in individuals with chronic stroke [62,63]. More recent randomized pilot studies have corroborated these findings in subacute stroke populations, reporting improvements in upper-limb function and task performance following taVNS treatment [64]. Notably, taVNS has also been associated with reductions in post-stroke depression symptoms and may contribute to cognitive and motor gains when administered alongside physical therapy [51].

The proposed mechanism by which VNS supports motor recovery involves its modulation of key neuromodulatory circuits, particularly those governing the release of norepinephrine, acetylcholine, and BDNF from regions such as the locus coeruleus and basal forebrain. These substances are known to enhance synaptic plasticity, a core process in cortical reorganization following stroke. Supporting evidence from fMRI studies has shown that taVNS produces distinct patterns of motor cortex activation, influenced by both the side of ear stimulation and the location of the brain lesion, suggesting that individualized stimulation parameters could further improve therapeutic outcomes [65].

In summary, both implanted and non-invasive VNS modalities present promising approaches to augment post-stroke rehabilitation. When paired with goal-directed motor practice, VNS appears to promote activity-dependent neuroplasticity, thereby facilitating more meaningful and sustained functional recovery.

CHAPTER 3: Emerging and Investigational Applications

1) Inflammatory and Autoimmune Diseases (e.g. Crohn's Disease, Rheumatoid Arthritis)

Crohn's disease is a nonspecific, chronic inflammatory disorder primarily affecting the gastrointestinal tract. As an incurable disease with a relapsing and progressive course, it imposes a substantial burden on patients' quality of. It most frequently involves the terminal ileum (ileum terminale) and the colon. The pathological process is transmural, which predisposes patients to complications such as strictures, fistulae, and intra-abdominal abscesses. These complications often necessitate surgical interventions, which remain a common consequence of advanced disease. The current therapeutic paradigm emphasizes achieving deep remission in order avert complications [66]. While conventional therapies constitute the mainstay of treatment, growing attention is being directed toward innovative approaches as a VNS due to its potential to modulate systemic inflammatory responses. A particularly intriguing area of research of Crohn's Disease's pathogenesis is the malfunction of the brain–gut microbiota (BGM) axis, a bidirectional communication network that integrates neural, hormonal, and immunological signalling pathways. Increasing evidence suggests robust interactions between the neurons of the enteric nervous system (ENS) and intestinal glial cells, as well as between the intestinal epithelium and the ENS, all of which contribute to the maintenance of epithelial barrier integrity and regulation of local immune responses [67]. Homeostasis of the gut microbiome is critical for maintaining overall systemic balance. A growing body of literature postulates that the microbiota exerts its neuromodulatory effects on the central nervous system via the vagus nerve [68]. The anti-inflammatory properties of VNS continue to be elucidated through experimental and clinical research. A central mechanism involves the attenuation of pro-inflammatory cytokine release—particularly IL-6, IL-1β, and TNF-α.

RA is another chronic autoimmune condition marked by persistent synovial inflammation, progressive destruction of cartilage and bone, and eventual disability. Affecting approximately 0.5–1% of the general population, RA primarily targets joints, although extra-articular manifestations are also common [69]. The potential benefits of VNS in RA have garnered increasing interest. Experimental studies indicate that inhibition of α7nAChR in synoviocytes enhances the release of pro-inflammatory mediators. In animal models of RA, any activation of α7nAChR resulted in a marked reduction in arthritis activity. Furthermore, clinical investigations

have observed significant reductions in TNF production in peripheral blood samples collected from RA patients 42 days following VNS. While these findings are promising, additional randomized controlled trials are required to definitively establish the efficacy and safety of VNS in RA management. If confirmed, VNS may represent a valuable adjunct or alternative to long-term immunosuppressive therapy, which is often associated with considerable adverse effects and long-term toxicity [70].

2) Cardiovascular Disorders (e.g., Heart Failure, Atrial Fibrillation)

HF is a set of symptoms, which causes a decrease in the quality and length of life [71]. The heart is unable to pump the right amount of blood to the organs of our body, so that too little oxygen reaches the individual organs necessary for their functioning. Heart function is possible thanks to the function of the heart muscle and the conduction system. Both are innervated by the vagus nerve. Due to the well-known mechanisms of the effect of vagus nerve on heart function, the possibility of using VNS as a form of therapy in cardiological diseases is being investigated. These studies are conducted on various models. Excessive activation of the sympathetic part of the autonomic nervous system may be an important pathogenetic factor in the development of left ventricular diastolic. Preclinical studies have shown that transcranial VNS leads to significant improvement of left ventricular hemodynamic parameters in animal models of HF, while reducing mortality from 50% to 14% [72]. In addition, VNS has been shown in numerous animal models to inhibit ventricular arrhythmias, myocardial structural remodelling, and sudden cardiac death, while improving left ventricular contractile function. The effect on cardiac remodeling in HF is also being studied [73].

One study showed that therapy with the VNS resulted in an improvement in the left ventricular ejection fraction (LVEF), prevented progressive dilatation of the left ventricular cavity, and had a beneficial effect on the levels of biomarkers of HF compared to the control group. However, it was found that achieving lasting therapeutic effects requires chronic use of VNS – in the discussed study the intervention was conducted for a period of 6 months and after the end of therapy after 3 months, the recurrence of HF symptoms was observed to values close to the initial ones [73]. In another study, INOVATE-HF, 707 patients were monitored for several months. Although no statistically significant differences were demonstrated in overall mortality, HF-related cardiovascular events, or reverse myocardial remodelling, VNS was associated with significant improvements in the 6-minute walk test, reductions in New York Heart Association (NYHA) functional class, and improvements in quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire. A separate study demonstrated that vagal

electrical stimulation combined with beta-blocker therapy resulted in a greater improvement in LVEF than beta-blockers alone. However, the results of studies evaluating the use of VNS in patients with HF are not unequivocal. Some of them show that VNS did not improve the risk of death or HF events in patients with HF with reduced ejection fraction (HFrEF) [74]. Studies on isolated, non-denervated hearts have shown abundant vagal innervation within the heart ventricles, which may provide a basis for using this zone to protect against ventricular fibrillation. This protection may be due to the release of nitrous oxide (NO) by an independent nitrergic neural network, which has been proven in studies [75].

Atrial fibrillation (AF), a common arrhythmia characterized by an uncoordinated excitation of the atria, which may be accompanied by rapid ventricular response. Despite its high incidence, the treatment of AF has not yet been optimized [76]. Although the exact pathophysiology of AF has not yet been fully elucidated, it is said that factors related to the balance of sympathetic and parasympathetic tone have an impact on the development of this arrhythmia. Therefore, the use of VNS in the treatment of AF is the subject of research. Chronic overactivation of the sympathetic nervous system has been associated with an increased risk of developing and exacerbating AF [77]. Some studies suggest that electrical and autonomic remodelling may interact to increase the likelihood of developing AF. The study showed that VNS was able to inhibit both electrical and autonomic remodelling processes of the heart and also reduced the risk of developing AF [78]. These effects have been attributed to the ability of VNS to modulate the autonomic nervous system of the heart, inhibiting its abnormal activity. According to the results of one study, VNS showed a significant effect on the induction and duration of AF [79].

3) Metabolic and Endocrine Disorders (e.g., Obesity, Type 2 Diabetes)

The vagus nerve constitutes a critical component of the parasympathetic nervous system and is primarily responsible for providing extensive innervation to visceral organs, particularly within the gastrointestinal tract. Among its various roles, the vagus nerve plays a pivotal part in modulating satiety and feeding behaviour, as well as in maintaining short-term energy balance by modulating appetite and controlling food intake [80].

A body mass index (BMI) equal to or exceeding 30 kg/m^2 constitutes the diagnostic threshold for obesity. Over recent decades, the incidence of obesity has escalated alarmingly across the globe. There are plenty of factors that synergistically contribute to the dysregulation of appetite control and metabolic imbalance [81]. Experimental

studies involving both human and animal models have revealed that prolonged exposure to obesogenic environments, such as high-fat diets, compromises the sensitivity of vagal afferent neurons to gastrointestinal peptides and stretch signals. This attenuated neural responsiveness implies that the vagus nerve's capacity to transmit satiety signals becomes progressively impaired [80]. In preclinical experimental models, the implantation of the VNS electrodes has demonstrated promising metabolic outcomes. It was associated with notable reductions in caloric intake, enhanced satiety signalling, and increased energy expenditure. Some of the experiments show, that the degree of weight loss appeared to be positively correlated with both the initial BMI and the frequency of electrical stimulation [82]. Despite these encouraging results, the role of VNS in weight modulation remains a topic of scientific debate. Contradictory reports in the literature highlight the heterogeneity of therapeutic outcomes, with some studies failing to confirm statistically significant metabolic benefits [83].

Diabetes mellitus constitutes a heterogeneous group of chronic metabolic disorders unified by the presence of persistent hyperglycaemia, which arises due to deficiencies in insulin secretion, resistance to insulin action, or both [84]. Despite substantial advancements in antidiabetic pharmacotherapy, achieving and maintaining glycaemic control in patients with type 2 diabetes remains an ongoing challenge in routine clinical practice. Given the vagus nerve's central role in modulating glucose, a number of preclinical studies have explored the therapeutic utility of VNS in glycaemic control. Findings suggest that certain stimulation protocols, can induce acute hyperglycaemia, although associated changes in insulin levels often fail to reach statistical significance [85]. Taken together, these findings underscore the nascent state of research into VNS-based interventions for metabolic disorders. While preliminary data indicate potential therapeutic avenues, particularly in obesity and type 2 diabetes, conclusive evidence remains elusive. Thus, further mechanistic studies and well-designed clinical trials are essential to delineate the true clinical utility of the VNS in metabolic disease modulation.

4) Psychiatric and Neurodevelopmental Disorders (e.g., PTSD, Anxiety, Autism Spectrum Disorders)

The first experimental findings of antiepileptic effect of VNS opened the path for further investigations into the neuromodulatory role of the vagus nerve. In subsequent years, additional preclinical studies provided compelling evidence that VNS induces significant changes in the bioelectric activity of the brain [86]. Beyond epilepsy, VNS has shown promising therapeutic potential in the management of anxiety-related disorders, including posttraumatic stress disorder (PTSD). Experimental studies conducted in rodent models, particularly rats, have demonstrated that VNS enhances the extinction of conditioned fear responses and attenuates anxiety-like behaviours under conditions of moderate stress, suggesting its potential anxiolytic

properties [87]. The results of a prospective clinical trial designed to assess this effect in a therapeutic setting, demonstrated significant and clinically meaningful improvements in key metrics of PTSD symptom severity. Importantly, the therapeutic effect of the VNS was durable [88].

Furthermore, accumulating scientific evidence highlights the potential application of VNS in the treatment of neurodevelopmental disorders, particularly autism spectrum disorder (ASD). Individuals with ASD frequently exhibit parasympathetic dysregulation, manifested by reduced vagal tone and autonomic inflexibility, which are believed to contribute to core behavioural, emotional, and cognitive impairments observed in this population [89]. The findings of an a clinical trial revealed that 56% of patients without ASD experienced a ≥50% reduction in seizure frequency. In addition to the seizure-related outcomes, they reported notable improvements in several neurocognitive and functional domains, including heightened alertness, enhanced verbal communication, improved memory, and greater educational and occupational performance [90].

5) Cognitive and Neurodegenerative Conditions (e.g., Parkinson's Disease, Alzheimer's Disease)

Reduced vagal tone is frequently observed in individuals with neurodevelopmental disorders, and the available literature suggests that VNS may act to compensate for the underactivity of vagal afferent signalling pathways, thereby restoring homeostatic autonomic balance. Numerous clinical studies also indicate significant and sustained improvement in the overall quality of life in patients with neurodevelopmental disorders following the initiation of VNS therapy [89]. Additionally, positive therapeutic effects of VNS have been observed in certain studies focused on girls with Rett syndrome, a severe X-linked neurodevelopmental disorder associated with mutations in the methyl-CpG binding protein 2 (MECP2) gene [91]. In these cases, VNS has been linked with reductions in seizure frequency, as well as potential improvements in motor function and behavioural regulation and other as a Parkinson's disease (PD).

VNS appears to modulate cortical activity and exert a stabilizing effect on motor performance in PD. It has demonstrated a beneficial impact on multiple gait-related parameters, facilitating more coordinated and stable locomotor patterns in affected individuals. It should be noted, that not all results it this matter have been positive. In several assessments, no statistically

significant improvements were observed. Moreover, neuroimaging studies revealed a statistically significant decrease in hemodynamic responses within the left primary somatosensory cortex following completion of the VNS protocol, raising questions about the specificity and consistency of central nervous system engagement by this modality [92].

Increasing scientific attention is being directed toward the interaction between VNS and the BGM axis, especially in the context of neurodegenerative diseases such as Alzheimer's disease (AD). There is growing evidence supporting the hypothesis that disruption of this bidirectional communication system may play a role in the pathogenesis of AD [93]. The electrical stimulation of the vagus nerve has the potential to modulate the flow of signals along this axis, thereby exerting therapeutic effects on the clinical symptoms or progression of AD [94]. Furthermore, stimulation of the vagus nerve is known to induce the release of critical and neurotrophic factors, both of which are thought to play vital roles in neuronal survival, synaptic plasticity, and cognitive function [93].

CHAPTER 4: Safety, Tolerability, and Adverse Effects

The most thoroughly studied and clinically established indication for VNS remains its use in patients with DRE. Since its clinical introduction, more than 10,000 individuals have undergone VNS implantation, with data from as early as 2001 supporting its widespread adoption. However, updated global estimates regarding the total number of treated patients remain unavailable [95].

In the initial years of VNS implementation, several complications were reported, such as transient facial muscle weakness and mechanical failures including electrode fracture. These early adverse events have been significantly reduced through improvements in both device design and surgical techniques. During active stimulation, commonly encountered side effects include voice alteration—affecting approximately 55–60% of recipients—paraesthesia (15–25%), and coughing (observed in 15–20%) [95]. These symptoms typically abate over time or become manageable through adjustments in stimulation parameters and rarely necessitate therapy discontinuation. Furthermore, in the context of chronic inflammatory conditions such as HF, the safety profile of VNS is comparable to that observed in neurologic applications [74].

Among the most serious risks associated with VNS is bradycardia, which may in rare cases progress to asystole [95]. While the majority of such events have been recorded

intraoperatively during implantation, there are isolated reports of cardiac arrest occurring during long-term therapy in patients with epilepsy [96].

Infectious complications following VNS implantation occur in an estimated 3–6% of cases and, in more severe presentations, may necessitate device removal. Another noteworthy, though typically transient, postoperative issue involves unilateral lower facial weakness, likely attributable to the extent of surgical exposure required for lead placement. The precise pathophysiology remains unclear, but increased surgical experience has markedly reduced the incidence of this complication over time [95].

There are also technical limitations linked to diagnostic imaging in VNS recipients. For instance, MRI of the thoracic region is contraindicated due to the potential for wire heating, which may damage the device or surrounding tissue. Similar contraindications apply to therapeutic diathermy modalities. Nevertheless, several studies have documented VNS use without reports of serious adverse outcomes, infection, or participant withdrawal from therapeutic protocols [97].

Overall, VNS is generally well tolerated, with adverse effects typically mild to moderate in intensity. These may include hoarseness, dry throat, shortness of breath, or localised paraesthesia in the region of the surgical incision [70]. Importantly, VNS does not elicit many of the systemic side effects commonly associated with pharmacologic treatments—such as fatigue, psychomotor slowing, or anxiety. This gives VNS a favourable tolerability profile that compares well to modern antiepileptic agents [95]. One of the most important recent developments in this field is the emergence of non-invasive stimulation modalities such as taVNS, which offer the promise of further improving safety and accessibility [93].

CHAPTER 5: Future Directions and Challenges

1) Biomarkers and Personalized Approaches

The limited number of randomized clinical trials currently hinders the identification of reliable biomarkers for predicting treatment outcomes and determining eligibility for VNS therapy. It remains unclear why some individuals benefit significantly from the treatment while others show little to no improvement. As such, identifying biomarkers capable of forecasting the clinical efficacy of VNS across various disorders is a pressing research priority.

Efforts have been made to determine predictive factors for VNS responsiveness in patients with DRE. One study, involving 59 individuals with DRE and 50 healthy participants, found that higher levels of HRV before surgery were associated with better post-treatment outcomes. Among patients with DRE, HRV values were generally elevated during sleep compared to wakefulness, aligning with established patterns of circadian autonomic regulation [98,99]. Those classified as responders—defined as achieving a reduction of more than 50% in seizure frequency—demonstrated significantly higher baseline HRV than non-responders. These findings suggest that preserved parasympathetic function, reflected in higher HRV, may enhance the neuromodulatory impact of VNS, positioning HRV as a promising predictive marker [98].

Similar results were observed by Liu et al. in a study of 32 DRE patients and 32 healthy controls, where individuals who responded positively to VNS also exhibited higher HRV at baseline [100]. Given the invasive nature and substantial cost of VNS therapy, such predictive indicators could prove valuable in guiding clinical decisions and patient selection.

VNS has also been shown to exert anti-inflammatory effects. In a study by Berthon et al., stimulation of the vagus nerve was found to suppress the production of pro-inflammatory cytokines—including TNF, IL-1β, and IL-6—in human subjects [101]. This retrospective investigation also assessed individuals with RA, demonstrating both a reduction in TNF levels and clinical improvement following VNS treatment. Similarly, Qi et al. reported decreased IL-8 production from peripheral blood mononuclear cells (PBMCs) post-stimulation [102]. These findings support the possibility of tailoring VNS protocols to individual patients by monitoring inflammatory markers such as cytokine and TNF levels. Age has also emerged as a significant factor influencing VNS efficacy.

According to Lagae et al., in a cohort ranging from 19 months to 25 years of age, children under the age of five showed the most substantial improvement, with 77% achieving seizure reductions of at least 50%. Notably, three of the four patients who became completely seizure-free belonged to this youngest subgroup. The association between younger age and favorable outcomes was statistically significant ($p < 0.006$) [103].

In addition, genetic research has uncovered associations between specific single nucleotide polymorphisms (SNPs) and treatment success. Variants in genes encoding adenosine kinase (ADK), ecto-5′-nucleotidase (NT5E), and the adenosine A1 receptor (A1R) were found to correlate with better clinical responses. Among patients carrying advantageous genotypes (such as the AA variant of ADK rs11001109) 100% achieved more than 50% seizure reduction,

and 40% experienced complete seizure remission [104]. These insights highlight the potential for genetically guided, personalized VNS therapy in the future.

2) Advances in Closed-loop and Adaptive VNS

VNS technologies can generally be divided into three categories: open-loop, closed-loop, and adaptive systems.

In the open-loop configuration, stimulation is delivered according to a pre-set schedule that remains independent of the patient's real-time physiological state. The device emits electrical pulses based on a fixed duty cycle, and physicians can adjust parameters such as current amplitude, pulse width, frequency, and the duration of ON and OFF phases. However, these settings are static and do not adapt to moment-to-moment changes in neural or bodily activity. The only form of semi-adaptive input from the patient is manual activation via a magnet when they sense an impending seizure [105]. The first commercially available system of this kind was the NeuroCybernetic Prosthesis (NCP), introduced with the Model 100 (M100) stimulator, which received FDA approval for treating drug-resistant epilepsy in 1997 [21,106].

Closed-loop VNS represents a more advanced and responsive form of neuromodulation. These systems continuously monitor specific physiological signals—such as heart rate, HRV, or EEG—and use this feedback to tailor the stimulation in real time, based on the patient's current clinical state. Unlike open-loop devices that deliver stimulation regardless of context, closed-loop systems analyze biological indicators and activate only when a need is detected, thereby offering a more timely and precise therapeutic response [107]. This reactive model allows for the minimization of unnecessary stimulation, potentially reducing side effects and improving overall tolerability [108].

The most sophisticated form of this technology is adaptive VNS. These systems go beyond simple feedback mechanisms and incorporate learning algorithms capable of recognizing individual patient patterns. Adaptive VNS adjusts stimulation parameters dynamically by integrating a wide range of data sources, including EEG readings, heart rate, HRV, sleep quality, physical activity, prior episodes of illness, and the body's previous responses to stimulation. It may also factor in environmental and behavioral influences such as circadian rhythms and stress levels. At the core of adaptive systems are machine learning (ML) algorithms, which identify complex patterns in physiological data and predict the likelihood of symptom exacerbation. Despite their potential, adaptive VNS technologies face significant

limitations. Current research is still in its infancy, with most studies relying on small patient cohorts or animal models. Furthermore, implementing ML-driven systems requires access to extensive datasets, significant processing capabilities, and continuous physiological monitoring—placing high demands on both the hardware and clinical infrastructure required for deployment [105,109]. The summary and comparison of different VNS methods is presented in Table_1.

VNS Method	Control Type	Description	Advantages	Disadvantages
Open-loop VNS	No feedback	Stimulation is delivered at fixed intervals regardless of the patient's state	Simple implementation, FDA-approved, good tolerability	Low precision, no response to physiological changes
Closed-loop VNS	Reactive feedback	Stimulation is triggered by specific physiological signals (e.g., EEG, HRV)	Higher efficacy, reduced unnecessary stimulation	More complex, requires sensors and signal processing
Adaptive VNS	Dynamic feedback	Parameters (e.g., intensity, frequency) are continuously adjusted in real time	Potentially highest efficacy, personalized therapy	Still under research, technically demanding

Table_1 The comparison of different VNS methods

3) Ethical and Regulatory Considerations

As neuromodulation technologies like VNS continue to evolve, they raise a variety of ethical and regulatory concerns—particularly as newer systems incorporate AI, machine learning algorithms, and multimodal physiological monitoring. These issues are relevant not only to traditional devices but also to more advanced and autonomous stimulation platforms.

Informed consent and patient autonomy remain fundamental ethical pillars in the application of VNS. Patients must fully understand the implications of device implantation and the potential long-term effects of stimulation. This issue becomes especially complex in the treatment of psychiatric conditions, where patients may have impaired decision-making capacity. Ethical dilemmas may also arise if a patient initially consents to treatment but later loses the ability to

make autonomous choices. In adaptive VNS systems that operate with a degree of independence, patients must be made fully aware of how the algorithms function, what data is collected, and what limitations exist within the technology [110,111].

Data privacy and security are also critical concerns, especially in adaptive systems that require continuous collection and processing of sensitive biological data—including EEG signals, heart rate, sleep cycles, and physical activity. These technologies must comply with data protection regulations such as the General Data Protection Regulation (GDPR) in the European Union. Key questions include who owns the data, who can access it, and how it is stored and protected.

The **opacity of AI-based decision-making** introduces additional challenges. In many machine learning systems, the reasoning behind therapeutic adjustments may not be transparent, even to clinicians. This lack of interpretability necessitates the development of "explainable AI," ensuring that healthcare providers and patients can understand and evaluate how decisions are made. It also raises the issue of accountability: if an autonomous system causes harm, it must be clear whether the responsibility lies with the manufacturer, the healthcare provider, or the algorithm itself.

Another pressing issue is **equitable access** to advanced VNS systems. As technologies become more sophisticated and costly—particularly those involving AI-driven personalization—there is a risk that socioeconomic disparities will widen. This underscores the need for well-defined reimbursement policies, cost-benefit analyses, and transparent eligibility criteria to ensure fair access to treatment.

Finally, **regulatory approval and oversight** present significant challenges. All VNS devices must pass through rigorous assessment by authorities such as the FDA (U.S.) or European Medicines Agency (EMA) (EU). Newer adaptive systems that rely on dynamic, updateable software and AI components require ongoing risk assessments, software version tracking, and compliance with evolving medical device regulations—particularly those applicable to high-risk, Class III devices [112].

4) Knowledge Gaps and Research Priorities

Although the use of VNS has expanded across various neurological and psychiatric disorders, multiple aspects of its mechanisms, applications, and long-term effects remain insufficiently understood. This is particularly true for newer forms of stimulation—such as adaptive and closed-loop systems—that rely heavily on artificial intelligence and advanced

physiological monitoring. Key research priorities and existing knowledge gaps are outlined below.:

- **Mechanisms of action** – While it is established that VNS influences several brain regions, including the brainstem, thalamus, and limbic system, the exact neurophysiological mechanisms responsible for its therapeutic effects remain unclear. Further studies using neuroimaging techniques such as fMRI and PET, along with neurochemical investigations, are necessary to clarify how specific stimulation parameters affect neural circuits and activity [113].

- **Biomarkers of response** – There is a lack of validated biomarkers that can reliably predict which patients will benefit from VNS therapy. Although ongoing research explores various possibilities—such as EEG features, HRV, inflammatory cytokine profiles, and genetic markers—none of these have yet been integrated into standard clinical protocols.

- **Clinical evaluation of adaptive VNS** – Despite its theoretical advantages, adaptive VNS remains an experimental intervention. There is an urgent need for well-powered randomized controlled trials to evaluate its effectiveness and safety across a range of conditions, including epilepsy, depression, anxiety disorders, and neurodegenerative diseases.

- **Long-term safety** – Data on the long-term safety of VNS, particularly over periods longer than 10 years, is still limited. This gap is especially significant for pediatric populations and for individuals with comorbid medical conditions. Prospective longitudinal studies and patient registries are necessary to address these concerns.

- **Impact on quality of life and functional outcomes** – While much of the existing literature focuses on symptom reduction (e.g., seizure frequency), less attention has been paid to broader measures of quality of life. There is a need for studies that examine how VNS affects patients' daily functioning, social integration, employment prospects, and overall well-being.

- **Ethical and legal frameworks** – As adaptive VNS technologies evolve rapidly, ethical and legal standards must keep pace. There is a growing need for standardized regulations covering data privacy, algorithm accountability, and equitable access to therapy. Additionally, ethical challenges arise in clinical trials involving control groups, where

participants may be exposed to surgical risks without the prospect of receiving active stimulation [114].

CONCLUSIONS

1) Summary of Key Insights: Mechanisms, Technology, and Safety of VNS

VNS has evolved from a niche antiepileptic intervention into a versatile bioelectronic medicine platform capable of modulating neural, autonomic, and immune circuits. Both iVNS and nVNS engage afferent vagal pathways projecting to the nucleus tractus solitarius, locus coeruleus, and limbic-prefrontal networks, leading to widespread modulation of cortical excitability, neurotransmitter release, and HPA axis activity. Concurrently, activation of the CAP – via α7nAChR mediates suppression of pro-inflammatory cytokines, underpinning its immunomodulatory effects. Technological advancements have expanded stimulation modalities, from implanted cervical devices with programmable parameters and durable batteries to transcutaneous approaches offering non-invasive alternatives with reduced procedural risks. Emerging closed-loop and adaptive systems leverage physiological and behavioral feedback, including machine learning algorithms, to tailor stimulation dynamically, potentially enhancing efficacy while minimizing side effects and conserving device longevity.

Safety data collected over decades consistently demonstrate a favorable tolerability profile. The most frequent stimulation-related adverse effects—such as hoarseness, throat discomfort, and transient cough—are typically mild and manageable by adjusting parameters. Surgical complications have decreased due to improved techniques, with infections, lead fractures, vocal cord paresis, and arrhythmias now rare. Imaging limitations and restrictions on electromagnetic therapies persist but have lessened with newer device generations and the introduction of non-invasive methods, thereby widening patient eligibility.

2) Clinical and Research Implications

VNS has firmly established its role across multiple clinical indications. In drug-resistant epilepsy, responder rates (≥50% seizure reduction) range from 40 to 60%, including in pediatric populations with developmental encephalopathies. Treatment-resistant depression demonstrates meaningful response and remission rates alongside improvements in functionality and suicidality. Non-invasive VNS modalities have gained evidence for acute and preventive

migraine treatment and cluster headache relief, while paired VNS has shown promise in enhancing motor recovery post-stroke.

Beyond these approved uses, VNS shows potential in modulating inflammatory, cardiovascular, metabolic, and neuropsychiatric disorders. Preliminary data suggest benefits such as cytokine reduction in RA and Crohn's disease, autonomic rebalancing and improved exercise capacity in HF, anti-arrhythmic effects in AF, and metabolic improvements in obesity and type 2 diabetes. Early clinical trials indicate anxiolytic effects in PTSD, cognitive and autonomic gains in ASD, motor improvements in PD, and possible neuroprotective actions relevant to AD. While promising, these indications require confirmation through robust, sham-controlled studies.

3) Future Research Directions and Knowledge Gaps

To fully realize the potential of VNS, future research must address key gaps:

- **Biomarkers for personalized therapy:** Despite promising candidates—such as HRV, cytokine profiles, neuroimaging markers, and genetic polymorphisms—validated predictors of clinical response remain elusive.
- **Optimization of stimulation protocols:** Comparative investigations of invasive versus non-invasive, open-loop versus closed-loop, and diverse parameter settings are essential to define individualized treatment paradigms.
- **Long-term safety and pediatric data:** Extended follow-up studies, particularly in children and medically complex patients, are needed to elucidate long-term device durability, neurocognitive effects, and cardiovascular outcomes.
- **Integration with digital health and AI:** Cloud connectivity, wearable biosensors, and explainable AI-driven controllers hold promise for real-time monitoring and personalized titration but pose challenges in cybersecurity, data governance, and equitable access.
- **Ethical and regulatory frameworks:** The evolving landscape of adaptive VNS systems demands transparent validation, software version control, accountability standards, and rigorous informed consent, especially for vulnerable populations.

Continued interdisciplinary collaboration, standardized outcome measures, and open data sharing will be vital to bridge these knowledge gaps and facilitate evidence-based integration of VNS into broader clinical practice.

4) Final Remarks

Vagus nerve stimulation has matured into a clinically validated, mechanistically grounded, and technologically advanced therapeutic modality. Its favorable safety profile, expanding spectrum of indications, and potential for biomarker-guided personalization position VNS at the forefront of next-generation neuromodulation therapies. Realizing this potential will require sustained mechanistic research, ongoing technological innovation, and ethically guided implementation centered on patient well-being across neurological, psychiatric, and systemic diseases.

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Check: [MJ], [NS], [AG]

Formal analysis: [MK], [NS], [KK]

Investigation: [JS], [DZ], [JP]

Resources: [KK], [JP], [MO]

Data curation: [MG], [MO], [JS]

Writing-rough preparation: [MJ], [MK], [NS], [AG]

Writing-review and editing: [MK], [MG], [DZ], [JS]

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