Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Vagal nerve stimulation

Evidence Summary

(t)VNS may help restore balance to the autonomic nervous system, mitigate pain and inflammation, and enhance rehabilitation training. It is well-tolerated, but the optimal parameters for benefit are unclear.

Neuroprotective Benefit: (t)VNS may enhance task-specific learning and help normalize brain activity patterns in patients with neurological disorders, including epilepsy, depression, and possibly Alzheimer's disease.

Aging and related health concerns: (t)VNS may help rebalance the autonomic nervous system in conditions with sympathetic overactivation and reduce inflammation. It is particularly suited for motor and sensory rehabilitation training.

Safety: tVNS is generally considered safe for people without cardiac abnormalities, with stimulation site irritation as the most common side effect. Further studies aimed at optimizing stimulation parameters are needed.

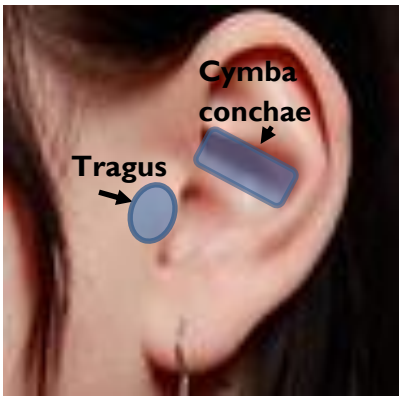
Availability: Rx	**Dose**: Optimal stimulation parameters for therapeutic benefit with tVNS have not been established. The most commonly used parameters use a pulse width of 250 or 500 µs, a frequency of 20-30Hz, and a current intensity to tolerability. 2-minute sessions for tVNS, and 30–60-minute sessions for taVNS.
Half-life: N/A	**BBB**: N/A
Clinical trials: tVNS has been tested in a variety of small pilot clinical trials for numerous conditions including Alzheimer's disease, epilepsy, depression, POTs, arthritis, tinnitus, IBS, POCD, stroke, brain injury, migraine, opioid withdrawal, insomnia, and long covid. VNS has been most extensively tested for its approved indications, epilepsy and major depression.	**Observational studies**: None

What is it?

Vagal nerve stimulation (VNS) involves electrical stimulation of the vagus nerve [1]. The vagus nerve is the 10th (X) cranial nerve containing both sensory afferent (80%) and motor efferent fibers (20%) which extend between the brainstem and various bodily organs, including the heart and digestive tract. It provides a network of communication between the brain and body to help maintain functional homeostasis by regulating the autonomic nervous system through its role as the primary driver of parasympathetic tone. The parasympathetic nervous system, often referred to as the 'rest and digest' system, promotes relaxation through the slowing of heart rate, which counters the sympathetic 'fight or flight' arm of the autonomic nervous system. VNS is designed to help restore balance in conditions with prominent autonomic nervous system dysfunction. Although it is only approved for a few indications, VNS has been tested in a variety of different disorders with a known or projected autonomic nervous system component. Traditional VNS involves the implantation of the electrical device in the neck along the left cervical branch of the vagus nerve.

VNS was initially approved by the European Commission in 1994, and by the FDA in 1997 for refractory focal epilepsy as an adjunct to anti-seizure medication. In 2005, VNS was approved for chronic or recurrent treatment-refractory depression in patients aged 18 and older.

In addition to this invasive form of VNS, non-invasive forms of transcutaneous VNS (tVNS) have recently been developed which stimulate the vagus nerve via electrodes placed on the skin, external to the nerve [2]. There are two primary forms of tVNS which differ based on the placement of the electrodes. ***Transcutaneous cervical VNS (tcVNS)*** places the electrodes along the side of the neck, to activate the cervical branch of the vagus nerve, similar to traditional VNS. The gammaCore Sapphire™ tcVNS device has FDA clearance for the treatment and prevention of migraine and cluster headaches. ***Transcutaneous auricular VNS (taVNS)*** places the electrodes on the ear to stimulate the auricular branch of the vagus nerve. The electrode is placed either on the tragus, which receives about 45% of its innervation from the vagus nerve, or on the cymba concha, which is 100% innervated by the vagus nerve.



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The NEMOS® taVNS device from Cerbomed GmbH has received the European CE mark for use in the treatment of epilepsy, depression, and pain. This device does not currently have FDA clearance for these indications. The company is now called tVNS Technologies GmbH, and the device is named the tVNS® L. ***Percutaneous nerve stimulation devices***, which stimulate a variety of nerves that innervate the ear, including the V, VII, IX and X cranial nerves and the occipital nerve, have also received FDA clearance, including the Bridge™ (formerly NSS-2 BRIDGE) and the IB-STIM, for opioid withdrawal and functional abdominal pain, respectively.

Neuroprotective Benefit: (t)VNS may enhance task-specific learning and help normalize brain activity patterns in patients with neurological disorders, including epilepsy, depression, and possibly Alzheimer's disease.

Types of evidence:

- 3 systematic reviews of studies assessing cognitive measures with VNS
- 1 meta-analysis of clinical studies assessing tVNS/VNS for postoperative complications
- 1 meta-analysis of clinical studies assessing cognitive measure with taVNS
- 1 meta-analysis of clinical studies performing brain imaging with tVNS
- 5 clinical studies assessing cognitive measures with taVNS
- 3 clinical studies using brain imaging with taVNS
- 2 clinical studies assessing cognitive measures and brain imaging with tcVNS
- 2 clinical trials testing VNS in Alzheimer's disease
- 1 RCT testing taVNS in mild cognitive impairment
- 1 clinical study using brain imaging with taVNS in mild cognitive impairment
- 1 RCT testing taVNS in postoperative cognitive decline
- 1 clinical study using brain imaging with VNS
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

The vagus nerve provides bidirectional information between the brain and bodily organs and thus is important for the maintenance of physiological homeostasis [3]. It is also a critical mediator of the autonomic nervous system, particularly the parasympathetic system. Vagal tone has been found to decline with aging, leading to an imbalance in the autonomic nervous system in favor of sympathetic activity, and can lead to a state of overall dyshomeostasis, which promotes the induction of inflammatory disorders [4]. VNS has been shown to facilitate vagal tone and the restoration of autonomic balance in a variety of small studies [1], suggesting that noninvasive VNS may mitigate age-related neuroinflammation, but to date there is no evidence regarding its ability to prevent dementia.

Due to its projections to brain regions involved in the regulation of neurotransmission associated with learning and memory, stimulation of the vagus nerve has been shown to impact task learning and retention [5]. A variety of studies have been conducted in populations of healthy volunteers

investigating different cognitive tasks, and utilizing different stimulation protocols. There has been a lack of consensus regarding an optimal stimulation protocol for the improvement of cognitive performance. Overall, the studies suggest that in individuals without neurodegenerative disease, vagal stimulation is most impactful in error reduction and that this approach does not enhance cognition globally, but rather, it improves performance in a task specific manner. As such, it likely has the greatest utility in facilitating the improvement of a particular skill or for neurorehabilitation (see aging section).

VNS: Cognitive outcomes in studies assessing invasive VNS have been mixed [6]. This may stem from the populations involved, which are primarily those with epilepsy or major depression, as well as the stimulation parameters used. Seizures and depression can both impact cognitive performance, thus an improvement in the underlying condition with VNS could potentially impact cognitive performance without having a direct effect on cognition per se. Additionally, the stimulation parameters typically used for epilepsy and depression differ from one another, neither of which were optimized for cognitive outcomes [7].

A systematic review assessed the impact of VNS in 13 studies that examined cognition [6]. Several studies indicated that VNS selectively impacted memory performance when administered during the memory consolidation phase. A study in epilepsy patients found that the impact of memory was dependent on current intensity, and showed an inverted U-shaped pattern, such that improvement was only seen at moderate intensities, while a slight detriment to performance was seen at the highest intensities. A similar pattern was observed in animal studies. A systematic review of 20 studies assessing the effects of invasive VNS on attention and working memory found that for epilepsy patients, the majority of studies showed evidence of improved attention or working memory following VNS, though the more rigorously designed RCTs were less likely to show effects [8]. The impact on attention for individuals with mood disorders was more variable. A systematic review of chronic (n=11) or acute (n=5) studies assessing VNS on cognition in patients with epilepsy found that the majority of chronic VNS studies showed no significant impact on cognition [9]. The impact to cognition in acute studies was variable depending on the outcome measures, such that VNS reduced errors, but impeded creativity. A clinical study in patients with refractory epilepsy implanted with a vagus nerve stimulator (n=21) undergoing VNS within a therapeutic range of 1.5 to 3mA underwent near-infrared spectroscopy imaging to assess change in cerebral blood flow in the frontal cortices in response to VNS [10]. Cerebral blood flow was altered in a stimulation intensity-dependent manner when VNS was coupled with a verbal fluency task, but only in patients who showed a therapeutic response to VNS. It is hypothesized that VNS may enhance cortical desynchronization through recruitment of the thalamocortical network and/or promote cortical plasticity.

tcVNS: In 21 healthy young adults (age 20-23 years), tcVNS was performed at a frequency of 25Hz, a pulse width of 0.5 ms, a current intensity of 2mA, and a voltage of 24V for active and 4.5V for sham [11]. The cognitive improvements were primarily seen within the memory, language, and attention domains. Active tcVNS stimulation impacted the number of errors or correct responses with respect to time on the verbal fluency test and Wisconsin card sorting test (WCST), such that there was an improvement in performance over time. Brain activity was monitored via fMRI, and activity in particular regions was found to be correlated with cognitive performance. On the WCST, there were associations between cognitive performance and altered neural activity in the right calcarine gyrus, left calcarine gyrus, right fusiform gyrus, left lingual gyrus, and right frontal gyrus. On the verbal fluency task, performance was associated with changes in the right fusiform gyrus, left fusiform gyrus and left calcarine gyrus.
A separate study of 30 healthy adults (age 18-54 years) also assessed cognitive performance in conjunction with fMRI neuroimaging in response to tcVNS using a protocol of 24V (4.5V for sham) at 5000Hz for 2 minutes at a repetition rate of 25Hz [12]. The electrodes were placed on the right lateral cervical area for active and the right anterior cervical area for sham. Active tcVNS stimulation was associated with better task accuracy and slower reaction times for difficult items on a matrix reasoning, as well as fewer false negatives on a forced-choice recognition task. The impact on performance may have been related to increased attention, but a distinctive tcVNS-associated neural activity pattern could not be identified in this study.

taVNS: A meta-analysis of 19 studies (n=718 participants) assessing cognitive measures in response to taVNS in healthy, predominantly young (age 18-30), adults found that taVNS primarily affected measures of executive function and accuracy [13]. It appears to be most influential on cognitively demanding tasks by increasing caution to reduce errors.
tVNS appears to be most useful in augmenting performance when applied in conjunction with training. In 18 healthy young (age 21-38 years) adult men, taVNS was applied to the left ear including the cavum concha and cymba concha, with a square waveform, pulse width of 180 µs, current intensity between 10 and 15mA, at either high (80Hz) or low (10Hz) frequency [14]. Olfactory tests were conducted before and after stimulation. Performance on the odor threshold test was not affected at either frequency, while performance on the supra-threshold test was improved following high frequency taVNS, in conjunction with activity changes in the contralateral (right) orbitofrontal cortex, as measured by near-infrared spectroscopy. The impact on performance in this study may have been tempered by the selection of frequencies, as the literature suggests that orbitofrontal cortex activation does not occur at 10Hz, single hemisphere activation is possible at 80Hz, while a more consistent bilateral activation

occurs around 20-30Hz. More simultaneous stimulation and imaging studies are needed to determine the optimal stimulation parameters to activate/modulate particular brain regions of interest.
In 30 healthy older adults (mean age 60.57 years), a single session of taVNS applied to the left tragus (or earlobe for sham) was performed using a frequency of 8Hz, pulse width of 200 µs, and current intensity of 5mA, during the encoding and consolidation phase of a face-name associative memory task [15]. Active taVNS led to higher rates of correct responses compared to sham, and the benefits were task specific. Notably, the effect of VNS was modified by the use of beta blocker antihypertensive medication, as those taking this medication had a less robust cognitive response. The blockade of noradrenergic receptors in the hippocampus by this type of medication may prevent the induction of cognitive benefits by tVNS.
In 24 young adults, taVNS applied to the left posterior tragus using square biphasic pulses with a 200 µs pulse width, 5Hz frequency, and current intensity tailored to tolerability during the reading of short passages resulted in greater passage memory recall relative to sham (earlobe) stimulation (49.63 ± 3.47% vs 37.04 ± 3.47) [16]. But, taVNS did not impact reading skill, such as reading rate or accuracy. In 58 healthy young men (mean age 19.5 ± 0.7 years) taVNS was combined with inhibitory control training using the Stop-Signal Task (SST) during three 60-minute sessions [17]. The active taVNS stimulation was applied to the cymba conchae of the left ear with a pulse width of 200-300 µs at a frequency of 25Hz with a biphasic pulse interval of 30s on and 30s off and current intensity tailored to detection without pain. The electrode was placed on the left earlobe in the sham condition. The combination of taVNS and inhibitory training resulted in significantly improved performance on the SST and a related response inhibitory task, the Go/No-go task, but had no significant impact on the performance of an unrelated conflict inhibitory task, the color-word Stroop task. Together, these studies suggest that taVNS may improve domain-specific learning, but has less potential for general learning.

The optimal stimulation parameters for cognition and learning have not been established, but there have been studies designed to assess the relationship between stimulation and brain activity patterns. A meta-analysis of four studies including 60 participants in which tVNS was performed using different sites of stimulation across the studies [18]. Overall, the studies showed a decrease in activity within the hippocampi and parahippocampal gyri, indicative of decreased limbic activity. This was coupled with an increase in activity within the frontal and temporal cortices and insula, which may mediate the anti-depressant and analgesic effects of tVNS. In patients with recurrent depression (n=15) treated with taVNS, changes in functional connectivity, as assessed by fMRI, between the globus pallidus and postcentral gyrus was correlated with improvements on depression scales [19]. Increased activity with tVNS was also seen in the caudate and putamen of the basal ganglia, which may strengthen autonomic

control [18]. The brain regions impacted by tVNS are consistent with those shown to be affected by invasive VNS, suggesting tVNS may be a reliable non-invasive alternative to traditional VNS. An imaging study used taVNS along the cymba conchae at a frequency of 24Hz, and current intensity to tolerability (range 0.2 to 2mA) in 17 healthy adults simultaneously with magnetoencephalography (MEG) [20]. To overcome interference, biphasic pulses were used. Across all six frequency bands assessed, active taVNS stimulation led to differential activity in the parahippocampal gyrus, brain stem, frontal lobe and temporal lobe, relative to sham (earlobe) stimulation. The affected brain regions were consistent across participants, however ,the degree of activation was heterogenous. Changes in cross-brain connection activity as well as beta and delta band energy were also seen with taVNS in patients in minimally conscious states [21]. Due to individual differences in nerve anatomy, vagal tone, and brain rhythms, variation in electrode placement or frequency may be needed to induce sufficient neural activation, suggesting that a personalized, rather than a standardized approach may be needed. One study attempted to determine whether taVNS stimulation at the tragus or cymba conchae was superior for the induction of cognitive effects and biomarkers of vagal activation in 42 healthy young adult volunteers [22]. No differences were seen across stimulation sites using a pulse width of 200-300 µs and frequency of 25Hz. However, due to differences in tolerability across the sites, the current intensity was higher for the tragus (mean 2.18mA) relative to the cymba conchae (0.94 mA). A meta-analysis of 19 taVNS studies indicated a stronger association for cognitive outcomes with tragus stimulation, however, due to the general use of higher intensities at the tragus, the supporting evidence was considered weak [13]. A key finding of this study, which has been noted in a variety of other studies as well, is that although it is the most commonly used site, the earlobe may not be an ideal sham site because stimulation at this site can also alter neural activity patterns, and depending on the innervation pattern of a given person, may overlap with the activity patterns seen with stimulation at vagal targeted sites.

Post operative cognitive decline: POTENTIAL BENEFIT

A double-blind, sham controlled RCT tested the ability of taVNS to prevent post operative cognitive decline (POCD), also known as delayed neurocognitive recovery (dNCR), in elderly patients (n=124) undergoing total joint arthroplasty surgery [23]. taVNS was administered to the left cymba conchae at a frequency of 10Hz, pulse width of 300 µs, and current intensity of tolerability without pain starting one hour before the induction of before anesthesia, until the end of the surgery. Active stimulation was associated with a reduced incidence of POCD relative to sham (earlobe) stimulation (10% vs 27.1%), as well as lower circulating blood levels of acetylcholinesterase and butyrylcholinesterase, which is indicative of higher levels of anti-inflammatory cholinergic signaling. taVNS was also associated with lower circulating levels of the pro-inflammatory cytokines, IL-6, HMGB1, and S100β. This suggests that

taVNS may prevent the development of POCD by mitigating the induction of pro-inflammatory signaling cascades. A meta-analysis of tVNS studies for postoperative complications found that tVNS treatment was associated with better cognition (Standardized mean difference [SMD] 1.74, 95% Confidence Interval [CI] 0.96 to 2.52), as well as reduced inflammation, based on circulating cytokines (SMD 1.31, 95% CI 0.45 to 2.18).

Human research to suggest benefits to patients with dementia:

Alzheimer's disease: POTENTIAL BENEFIT

The locus coeruleus appears to be one of the earliest brain regions affected by neuronal loss and pathology during the course of Alzheimer's disease (AD) [6]. This can alter the pattern of neuronal activity in the locus coeruleus from phasic to tonic, and a disruption in the release of neurotransmitters to downstream brain networks, including those that are involved in learning and memory. VNS has been proposed as a mechanism to help restore locus coeruleus activity patterns and neurotransmission in AD patients.

Invasive VNS was tested in AD patients in a small pilot study twenty years ago [24]. Although this study lacked a control group, it provided proof-of-principle for a potential benefit to cognition with VNS. In the open-label pilot study ten AD patients were implanted with a vagus stimulator, and a two-week VNS adjustment period was initiated two weeks after implantation, then the VNS study protocol (current: 0.25mA, frequency: 20Hz, pulse width 500 µs, on/off 30 sec/5 min) was performed for eight weeks. In this acute phase, seven out of the ten patients were classified as responders based on improvement on cognitive assessments, the ADAS-Cog (median 3 points), and nine out of ten showed improvement on the Mini-Mental State Examination (MMSE) (median 1.5 points). A long-term phase continuation of the study including a total of 17 AD patients found that at six months, 76.5% (13/17) showed improvement or no decline on the ADAS-Cog (median 3 points), and 70.6% (12/17) showed improvement or no decline on the MMSE (median 2 points) [25]. By one year, the numbers for improvement or no decline were 7 out of 17 on the ADAS-Cog, 12 out of 17 on the MMSE, and 12 out of 17 on the Clinician's Interview-Based Impression of Change plus (CIBIC+). Additionally, there was no significant decline in mood or quality of life measures over one year. There was a median decrease of cerebrospinal fluid (CSF) tau by 4.8%, but an increase in phosphorylated tau by 5% over this period. Although, without a control group, the degree of potential benefit is hard to interpret.

More recently, a double-blind, sham controlled, RCT tested taVNS in 52 mild cognitive impairment (MCI)patients for 24 weeks [26]. In the active stimulation condition, a pair of auricular acupoints within the distribution of the vagus nerve, the left conchae (CO15) and CO10 were used, whereas the sham

condition used acupoints along the left scapha port of the ear, which is not innervated by the vagus nerve. The stimulation protocol used a current intensity based on tolerability ranging from 0.6 to 1.0 mA, with a pulse train of 20Hz for 10 seconds and 100Hz for 50 seconds each minute for 30-minute sessions, twice per day, five days per week. At the end of the study, there was a significant difference between the active and sham groups on the primary outcome, the overall scores of the Montreal Cognitive Assessment Basic (MoCA-B) cognitive assessment, with a mean improvement of 3.24 points in the active and 0.33 points in the sham. There were also significant improvements on the N5 (immediate recall) (mean improvement 1.6 vs 0.593 points) and N7 (delayed recall) (mean improvement 2.48 vs 0.815 points) parts of the Auditory Verbal Learning Test-Huashan version (AVLT-H), which assesses memory function. However, there were no significant improvements on the shape trails test A&B, Boston naming test, Pittsburgh sleep index scale (PSQI), REM sleep behavior disorder screening questionnaire, Epworth sleepiness scale, and functional activities questionnaire assessments between active and sham following treatment. While there were some statistically significant effects, it is unclear whether they would offer clinically meaningful improvement. Additionally, it is not known how long stimulation would be needed in order to see a meaningful impact on cognition, but based on the use of VNS in other neurological conditions, it may take at least 18 months for the development of stable changes in neuroplasticity which may underlie neurological benefit. The durability of the response is also unclear, such as if and how quickly cognition or brain patterns would revert upon tVNS cessation. Furthermore, as is the case with tVNS generally, the optimal stimulation parameters for AD or cognition have not yet been established.

A neuroimaging study in 50 patients with MCI investigated the impact of taVNS on functional connectivity in the brain using resting-state fMRI [27]. In this study, the auricular branch of the vagus nerve was stimulated using an electrode attached to the tragus of the left ear, while it was attached to the left earlobe in the sham group. The stimulation parameters used a current intensity of tolerability up to 10mA, with a frequency of 20Hz and a pulse width of 50 μs. Active taVNS stimulation was found to alter functional connectivity between brain regions, particularly those involved in salience and semantic functions. There was evidence for increased connectivity from the hippocampus to the prefrontal cortex and cingulate, with decreased connectivity to the anterior and medial temporal lobe. These changes may reflect a normalization of brain activity patterns, and the networks affected are those which underlie the cognitive processes most consistently impacted by VNS.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

The primary mechanism through which VNS is thought to promote cognitive function is through the regulation of adrenergic and cholinergic neurotransmission. The afferent fibers of the vagus nerve synapse onto nuclei in the brainstem, primarily the nucleus of the solitary tract, which is involved in the integration of peripheral sensory information [15]. These fibers then project to the locus coeruleus, which promotes the release of norepinephrine into brain regions associated with learning and memory, such as the hippocampus and prefrontal cortex [8; 27]. Imaging studies indicate changes in functional brain network activity in response to VNS. VNS has been shown to promote neuronal activation in the locus coeruleus [28], and microdialysis studies indicate that VNS can trigger the release of various neurotransmitters and neuromodulators, including acetylcholine, dopamine, norepinephrine, serotonin, and brain derived neurotrophic factor (BDNF) [8]. The stimulation protocol may influence the strength of activation within different functional networks, and thus moderate the observable impact to brain function. The inverted U-shaped relationship between VNS current intensity and memory performance is thought to stem from the effects of VNS on the release of norepinephrine from the locus coeruleus into cortical networks [7]. Stimulation that is too low fails to appreciably modify neurotransmitter release, moderate stimulation increases norepinephrine levels in a manner which promotes plasticity mechanisms to enhance learning in memory, while high stimulation leads to a dysregulation of norepinephrine signaling, which interferes with these cognitive processes [6]. VNS also increases levels of the neurotransmitter GABA, which is known to influence attention and executive function [8]. The alteration of activity within brain networks associated with memory, attention, and executive control via the modulation of neurotransmitter release is consistent with the observed impacts to cognitive performance following VNS in both preclinical and clinical studies. With respect to learning and memory, VNS appears to be most relevant during the memory consolidation phase.

The dysregulation of activity within the locus coeruleus may promote the accumulation of pathology in connected brain networks through an imbalance of inflammatory signaling. In addition to improving performance on measures of learning and memory, VNS has also been shown to reduce Aβ pathology and markers of neuroinflammation in AD models [29; 30]. The loss of norepinephrine is associated with increased Aβ deposition in the brain [27]. The activity of microglia and astrocytes is modulated by norepinephrine, such that norepinephrine promotes the production of BDNF and uptake of glutamate, while suppressing pro-inflammatory cytokine signaling [31]. The activation of vagal afferent fibers can also modulate the hypothalamic-pituitary-adrenal (HPA) axis and induce the cholinergic anti-inflammatory pathway which inhibits the production of pro-inflammatory cytokines by peripheral innate

immune cells [32]. The loss of vagal tone and locus coeruleus activity then tips the system in favor of pro-inflammatory signaling. The modulation of inflammatory signaling is thought to be one of the protective mechanisms of chronic VNS, however, clear evidence regarding the ability of VNS to modulate neuroinflammation in clinical studies has not yet been established.

APOE4 interactions: Not established

Aging and related health concerns: (t)VNS may help rebalance the autonomic nervous system in conditions with sympathetic overactivation and reduce inflammation. It is particularly suited for motor and sensory rehabilitation training.

Types of evidence:

- 1 meta-analysis of clinical studies using tVNS/VNS for post-operative pain/complications
- 1 meta-analysis of RCTs testing VNS for stroke rehabilitation
- 1 review of clinical trials using tcVNS for migraine/cluster headache
- 1 review of clinical studies testing tVNS/VNS for chronic pain disorders
- 1 review of clinical studies testing tVNS for tinnitus
- 1 review of clinical studies testing VNS for irritable bowel syndrome
- 1 review of clinical studies testing tVNS/VNS for postural tachycardia syndrome
- 3 clinical studies assessing serum cytokines with taVNS
- 2 clinical studies testing taVNS for insomnia
- 1 clinical study testing tcVNS for sleep deprivation
- 1 clinical study examining the effect of taVNS on brain-stomach coupling
- 1 clinical study testing taVNS on gastric motility
- 1 clinical trial testing tcVNS for gastroparesis
- 1 clinical trial testing VNS for rheumatoid arthritis
- 1 clinical trial testing tcVNS for rheumatoid arthritis
- 1 clinical trial testing taVNS for irritable bowel syndrome
- 1 clinical trial testing tcVNS for migraine
- 1 clinical trial testing tcVNS for opioid withdrawal
- 1 RCT testing taVNS for long covid
- Numerous laboratory studies

Pain: POTENTIAL BENEFIT

Vagal nerve stimulation has been shown to have analgesic properties under some conditions, which may depend on individual sensitivity and the stimulation parameters [2]. The mechanisms are not entirely clear, but thought to involve anti-inflammatory activity and the modulation of spinal circuits [33].

The gammaCore® tcVNS device has received FDA clearance for the treatment of migraine pain based on a series of clinical trials [34]. The gammaCore® device produces a 5kHz sine wave burst for 1 ms in duration lasting for 1 ms delivered at a frequency of 25Hz (1Hz for sham), with a 24V peak voltage and 60mA peak output current. The PRESTO trial included 248 patients with episodic migraine who received tcVNS stimulation within 20 minutes of migraine onset [35]. Active stimulation was associated with a higher degree of pain-free participants at 30, 60, and 120 minutes (Odds Ratio [OR] 2.3; 95% CI 1.2 to 4.4). The response rate (30.4%) was within the range seen for oral triptans or non-steroidal anti-inflammatory drugs (NSAIDs). tcVNS was not found to prevent migraines in the PREMIUM trial [34].

tcVNS was evaluated in the context of cluster headache in the ACT 1 and 2 trials, which showed significantly higher rates of acute pain reduction at 15 minutes for episodic cluster headaches (34.2% vs 10.6%). tcVNS did not significantly reduce pain for chronic cluster headaches but was associated with a reduction in their occurrence [34].

tcVNS stimulation using the gammaCore®, was also shown to reduce pain perception in patients with opioid use disorder undergoing opioid withdrawal (n=20) [36]. The efficacy on pain measures was associated with changes in respiration and heart rate variability, suggesting that the effect was mediated by the vagal stimulation. The NSS-2 BRIDGE device is a percutaneous nerve stimulator, which activates the auricular branches of the V, VII, IX and X (vagus nerve) cranial nerves as well as the occipital nerves, developed by Innovative Health Solutions (now NeurAxis) that was cleared by the FDA for use in the management of acute opioid withdrawal symptoms for five days. The Bridge™ device is now available through Masimo. These devices are highly touted by rehab clinics, but due to the absence of real-world data, their efficacy is unclear.

A meta-analysis of studies assessing tVNS in the context of postoperative pain found that VNS was associated with a reduction in pain (Standardized mean difference [SMD] 2.29, 95% CI 1.08 to 3.50; based on ten studies) [37]. VNS has also shown benefits in pilot studies in the context of other pain disorders, including fibromyalgia, and pelvic pain [33].

Inflammation: POTENTIAL ACTIVATION OF ANTI-INFLAMMATORY PATHWAYS

The induction of the cholinergic anti-inflammatory pathway is thought to be one of the primary mechanisms by which VNS confers benefit. Afferent vagal nerve fibers are activated and modulate the HPA axis to reduce inflammatory cytokine production in response to peripheral inflammatory stimuli,

such as elevated IL-1β [38]. However, the circulating profile of inflammatory mediators is highly context dependent, and thus can differ from person to person, which can make it difficult to assess acute changes in response to VNS. As a result, the impact of VNS on inflammatory mediators has been mixed across studies depending on the population, stimulation parameters, and timepoint of assessment. In preclinical rodent studies, the impact of VNS on cytokines has been shown to be stimulation intensity dependent. There may also be a frequency dependency, with low frequency stimulation allowing for more efficient induction of the anti-inflammatory cholinergic pathway. One study assessing the effect of an acute session of taVNS in young (n=20) and older (n=19) adults, found that after 30 minutes, active stimulation increased serum levels of IL-1β, IL-6, and IL-18, but not TNFα [38]. The protocol used stimulation parameters of a frequency of 30Hz, pulse width of 250 µs, and current intensity of 20mA applied to the left tragus. Discomfort due to the stimulation could have evoked an acute stress response, which could impact the cytokine milieu immediately after stimulation. Additionally, two other studies found no effect on TNFα levels within 90 minutes, but a decrease within 24 hours, suggesting that longitudinal cytokine profiling may be needed to accurately assess the anti-inflammatory impact of VNS.

The impact of VNS is generally more apparent in populations where inflammatory mediators are elevated at baseline. Inflammatory cytokine production following *ex vivo* activation of peripheral blood cells with the proinflammatory stimuli LPS or endotoxin was shown to be reduced in blood cells collected from epilepsy patients after VNS implantation [39; 40]. The induction of the inflammatory reflex was assessed in 17 patients with rheumatoid arthritis who underwent VNS treatment. Stimulation was delivered at a frequency of 10Hz, 250 µs pulse width, and current intensity to tolerability (0.25–2.0 mA) in 60 second intervals four times per day [40]. At day 46, TNFα production from their cultured peripheral blood was reduced, along with disease activity based on the Disease Activity Score 28 for Rheumatoid Arthritis with CRP (DAS28-CRP) score. IL-6 levels also correlated with therapy response. Notably, cytokine levels and disease activity tracked with stimulation, improving during on periods, and worsening during a 14-day hiatus period. The ability of tcVNS to impact inflammatory cytokines and disease activity in rheumatoid arthritis patients with high (n=16) or low (n=20) disease activity was tested in an open-label pilot study [41]. Stimulation was delivered to the right and left cervical vagus nerves using the gammaCore® device as a sine waveform (five sine waves, each lasting 200 µs) at a frequency of 25Hz, with a maximum current of 60mA, and voltage varied to tolerability (up to 24V) three times per day for four days. Twelve of the 16 patients with high disease activity showed improvement on the DAS28-CRP, along with a reduction in levels of C-reactive protein (CRP) and the cytokine IFN-γ, while effects were not apparent in those with low disease activity at baseline. Higher baseline disease activity was associated with lower cardiac vagal tone, which tracks with the stronger response to tcVNS

in this population. These studies suggest that chronic VNS may mitigate pathological inflammatory responses in conditions that involve autonomic nervous system dysregulation.

Rehabilitation: POTENTIAL BENEFIT WHEN PAIRED WITH TRAINING
VNS has been used to augment traditional rehabilitation exercises following neurological injuries, such as stroke. Paring stimulation with training in specific motor or sensory modalities appears to strengthen the effects of training. A meta-analysis of seven RCTs (n=236 participants) examined the impact of VNS in the context of stroke rehabilitation [42]. Upper limb sensorimotor function, as assessed by the Fugl-Meyer Assessment for Upper Extremity (FMA-UE) was found to show improvement at day 90 post-intervention (Standardized mean difference [SMD] 0.64, 95% CI 0.31 to 0.98; based on three RCTs). There was also an increase in the level of clinically meaningful upper limb sensorimotor function recovery, as defined by ≥6 points increase in FMA-UE (Risk Ratio [RR] 2.14, 95% CI 1.32 to 3.45). There was a medium to large effect size for the upper limb sensorimotor recovery (Hedges' g 0.535–2.659). There was not a clear consensus on the stimulation parameters, duration, or type (i.e. invasive vs non-invasive) of VNS needed for optimal benefit. The effect is hypothesized to be related to increased neuronal plasticity in the sensory and motor cortices in response to VNS.
Closed loop taVNS systems have recently been developed in which the stimulation process is regulated by biofeedback systems [43]. Motor activated taVNS (MAAVNS) pairs taVNS with motor activity, and was developed to enhance motor learning and rehabilitation. In this system, VNS is gated by muscle activity sensed by electromyography. Preclinical studies indicate that this type of stimulation improves motor neuron responses, and thus task performance, via the modulation of cholinergic signaling [44]. Respiratory gated taVNS (RAVANS) triggers stimulation during periods of exhalation but not during inhalation because inhalation is associated with transitory inhibition of the vagus nerve [43]. Thus far, this system has been tested primarily in the context of pain. Additional closed loop systems are under development which are designed to better align stimulation with the desired outcomes.

Tinnitus: POTENTIAL BENEFIT WHEN PAIRED WITH SOUND TRAINING
VNS has been tested in clinical studies for tinnitus as a form of sensory rehabilitation [45]. tVNS may be particularly suited for tinnitus because it has been shown to induce deactivation in the auditory cortex as well as the limbic system. Neuroimaging studies suggest that tinnitus patients have an overly strong connection between these brain regions, and that dampening the connection may be beneficial. The use of VNS is based on the premise that tinnitus stems from auditory cortex reorganization, which may not be a causal factor for all tinnitus patients. Clinically relevant improvements have not been readily apparent for the use of tVNS alone. However, tinnitus symptom reduction was seen in a variety of small

studies in which VNS (n=5) or tVNS (n=2) was paired with sound. These studies paired stimulation with pure tones excluding the tinnitus frequency. More studies are needed to determine whether tVNS can induce a durable response and if there is an optimal stimulation paradigm for efficacy.

Postural tachycardia syndrome: POTENTIAL BENEFIT FOR ORTHOSTATIC INTOLERANCE
Postural tachycardia syndrome (POTS) is characterized by orthostatic distress and in some cases may involve an imbalance between sympathetic and parasympathetic drive when in the supine position [46]. Thus, it has been hypothesized that activation of the parasympathetic nervous system, such as through vagal nerve stimulation may help correct this imbalance and reduce inflammation. tVNS has been tested for the alleviation of POTS symptoms in three pilot clinical trials.
One study tested acute taVNS to the right ear while supine and during a graded tilt in 14 patients with POTS. Relative to sham, active taVNS increased tilt time while reducing orthostatic tachycardia and the overall orthostatic hypotension symptom score [47]. However, the effects were dependent on the degree of vagal modulation at baseline, as those with low baseline vagal activity showed the greatest effect and those with high baseline vagal activity were generally non-responsive to taVNS. Another study aims to assess the impact of regular taVNS applied to the right cymba concha using the Nemos© device in POTS patients (NCT04632134) [46]. The stimulation parameters involve a frequency of 25Hz, a squared impulse waveform with a pulse width of 200 µs, at 30 second on/off intervals, with a current intensity to tolerability (mean 1.8mA±0.2) performed in one-hour blocks, four times per day for 14 days. This study utilizes the Composite Autonomic Symptom Score (COMPASS-31) tool to assess a wide array of dysautonomia symptoms. Data from nine patients shows significant reductions in orthostatic intolerance and gastrointestinal symptoms following stimulation, relative to baseline, as well as a blunting of heart rate elevation in response to standing. A randomized, double-blind, crossover study is ongoing testing the effect of taVNS at 50Hz during tilt table tests in combination with pyridostigmine or galantamine (cholinesterase inhibitors) on heart rate variability measures in 11 POTs patients (NCT03124355). Case reports have found evidence for improvement in symptoms of dysautonomia and orthostatic intolerance in patients receiving invasive VNS due to intractable epilepsy [46].
While the majority of taVNS studies use left side stimulation, there is evidence to suggest that for POTS and other conditions with a cardiac component, that right side stimulation may be more advantageous [13]. Although the lateralization is not as pronounced as in some other species, humans do appear to exhibit a right-side predominance for peripheral vascular sympathetic activity, and a modulation of neuro-cardiovascular sympathetic interactions by the right cerebral hemisphere. In terms of finding the optimal stimulation parameters, the use of heart rate variability measures may serve as a good readout biomarker.

Insomnia: POTENTIAL MINOR BENEFIT

The transition from wakefulness to sleep involves a shift from sympathetic drive to parasympathetic drive [48]. Due to the role of the vagus nerve in the facilitation of parasympathetic drive, VNS has been proposed as method to facilitate sleep in people with insomnia. In an RCT (n=30), taVNS to the concha area at a frequency of 20Hz, pulse width of 0.2 ms, and current intensity of mA for 20 minutes twice a day for one month was tested in patients with primary insomnia [49]. By the end of the study, the Pittsburgh Sleep Index Scale (PSQI) significantly decreased with taVNS, with 93.3% showing improvement, while 78.6% of those in the sham control group also had decreased PSQI scores. The effective response rate, defined as a ≥50% reduction on the PSQI, for the treatment group was higher (73%) than the control group (27%). A separate RCT involving 68 community-dwelling adults found that although there were significant improvements in global sleep scores on the PSQI following two weeks of at home taVNS, the effect was not significant relative to the sham control group [48]. This study used stimulation at the left tragus with a pulse width of 200–300 μs, current intensity to sensitivity, and frequency of 25Hz with no on/off cycles done over the course of four 4 hour per day, broken up into several time segments. The differences in stimulation parameters and duration may account for the weaker effects in the shorter study. Additionally, earlobe stimulation could potentially elicit a partial effect, depending on a given individual's aural innervation pattern.

A clinical study assessed the ability of tcVNS to improve cognitive performance in the context of sleep deprivation (34 hours of wakefulness) in 40 active military participants [50]. tcVNS was performed at a frequency of 25Hz with electrodes placed over the neck, two minutes per side, using the gammaCore® device. The active group performed better on measures of executive control on the Air Force–Multi-Attribute Task Battery and Psychomotor vigilance task, with benefits peaking at 12 hours post stimulation. Ratings of higher energy and lower fatigue were also reported, but no effects were seen for working memory, sustained attention, or mood.

Gastrointestinal disorders: POTENTIAL BENEFIT FOR IBS AND GASTROPARESIS

The vagus nerve innervates the digestive tract and provides parasympathetic drive. The vagus nerve has a bidirectional relationship with the gastrointestinal system and its microbiome [32]. The gut microbiota are responsive to endocrine secretions driven by vagal activity, while microbe secretions can also impact vagal activity. Due to its ability to activate the anti-inflammatory cholinergic pathway, which dampens the release of pro-inflammatory mediators by intestinal macrophages, VNS has been considered for inflammatory bowel diseases. There is some evidence to suggest sympathetic nervous system overactivation in individuals with inflammatory bowel diseases, which could potentially be ameliorated

by increasing parasympathetic drive through VNS [32]. Invasive VNS has been tested in pilot studies in patients with Crohn's disease [32]. These studies used low frequency stimulation (1-10Hz), which is thought to more potently activate anti-inflammatory efferent activity, relative to the higher frequency stimulation (20-30Hz) used for neurological disorders. Stimulation was needed for at least two months for benefits to be seen. In a 12-month study, deep (clinical–biological–endoscopic) remission was achieved by five out of nine patients, while in a 16-week study, four out of 16 patients showed remission, while seven had a partial response. These clinical effects were accompanied by decreases in inflammatory markers, such as calprotectin. taVNS was tested in a small open-label pilot study including three patients with irritable bowel disease (IBS) [51]. The study used stimulation at the left cymba and the cavum concha at 3Hz with a 250 µs pulse width for 30-minute sessions. Although there was a trend toward a reduction in IBS symptoms, this study was underpowered, and at four weeks, was likely also too short to determine whether taVNS can offer clinically meaningful benefit in this population.
The percutaneous electrical auricular nerve field stimulator, IB-STIM, which activates the vagus nerve, as well as other cranial nerves innervating the ear (V, VII, IX and X), has FDA clearance for the treatment of functional abdominal pain due to IBS in patients aged 11-18, up to 120 hours per week for three weeks. It has a unique FDA regulatory classification (CFR Title 21: 876.5340) and is similar to earlier versions of the device with FDA clearance developed by NeurAxis (formerly Innovative Health Solutions), including the NSS-2 BRIDGE.
VNS may also promote stomach-brain coupling, which provides signals of hunger and satiety. In a cross-over RCT, 31 healthy participants received taVNS to the right cymba conchae, or earlobe for sham, at 25Hz for 30 second on/off cycles [52]. Active stimulation increased brain-stomach coupling in the nucleus of the solitary tract, and the midbrain. Changes in brain coupling across the cortex were associated with changes in hunger state. VNS may also promote gastric motility, which may aid in gastric emptying. In an RCT, 57 healthy participants received taVNS at 25Hz or 1Hz stimulation to the left cymba conchae with a biphasic 250 µs pulse width, with 30 second on/off cycles [53]. The higher frequency stimulation promoted gastric motility, as measured by real-time gastric magnetic resonance imaging, by increasing the amplitude of the peristaltic waves. tcVNS using the gammaCore® device (two or three consecutive 2-minute stimulations to the right and left cervical vagus nerve three times per day) was tested in a pilot open-label trial in patients (n=23) with drug-refractory gastroparesis [54]. Following three weeks of treatment, 12 patients (52%) showed >30% decrease from baseline in Gastroparesis Cardinal Symptom Index (GCSI) symptoms, while 6 (26%) showed a >50% decrease, relative to baseline.

Long Covid: POTENTIAL BENEFIT FOR FATIGUE

A pilot double-blind, sham controlled RCT using taVNS was conducted in 12 individuals with long covid (NCT04638673) [55]. The taVNS was self-administered at home via two daily one-hour sessions with a frequency of 25Hz and pulse width of 500 μs at suprathreshold intensities six days per week for four weeks. The electrode node was placed on the cymba conchae of the ear, while the cathode was placed on the tragus. This proof-of-concept trial was not adequately powered to determine efficacy, but showed effects suggestive of improvement. In the two-week blinded phase, the number of predefined long covid symptoms (anxiety, depression, vertigo, loss of smell, loss of taste, headaches, fatigue, irritability, brain fog) reduced from 45% to 31% in the active group, but showed no improvement in the sham group (66% to 68%). The sham patients were crossed over into active treatment, and by week four, the average number of symptoms was 38% amongst all treated participants. Mental fatigue is the symptom that showed the clearest trend for improvement with taVNS across participants. Larger validation studies are needed.

BIOMARKERS

One of the major challenges of tVNS studies is an accurate assessment of the degree of vagal nerve activation. Several biomarkers have been proposed, though to date, none have been shown to be consistent and reliable.

Heart rate variability (HRV): Due to the vagus nerve's role as the primary mediator of parasympathetic innervation to the heart, activation of the vagus nerve can lower heart rate. However, due to the contribution of the sympathetic nervous system, heart rate on its on is not a reliable measure [56]. Instead, certain measures of heart rate variability are thought to be more reflective of vagal/parasympathetic activity. These include the root mean square of successive R-R interval differences (RMSSD), the percentage of consecutive R-R intervals differing by >x ms (pNNx, %), the respiratory sinus arrhythmia (RSA) and the high frequency (HF) spectral component of HRV, which can be derived from ECG measures [56]. A potentially complicating factor is the right-left asymmetry of cardiac-vagal activity. Animal studies indicate that right side VNS can reliably increase HRV, while the effects are inconsistent with left side VNS [56]. This may explain the lack of effect or inconsistent effects on HRV with VNS in humans, where it is almost always implanted along the left cervical branch. Since tVNS only activates afferent fibers, the effect of tVNS on HRV is indirect, which may lead to more heterogeneity. The effect of tVNS on HRV has been inconsistent across studies. A meta-analysis of 16 studies found that the evidence did not support an effect on HRV by taVNS [57]. The ability to detect an effect on HRV may be related to study parameters and baseline vagal tone. Changes in HRV measures tend to be most pronounced early during the course of stimulation, and studies that assess HRV

following taVNS of 10 minutes or less show the most consistent effects [58; 59]. Due to circadian regulation of the autonomic nervous system, tVNS-induced changes in HRV vary based on the time of day. While taVNS was found to increase RMSSD and HF power during both morning and evening, the effect was significantly higher with morning stimulation [59]. Several studies using HRV as an outcome measure for tVNS have found an association between response and baseline vagal tone/autonomic nervous system balance, suggesting that tVNS is most effective at enhancing vagal activity in a measurable manner when baseline activity is low [41; 46]. This may also account for the lack of effects seen in the majority of studies testing young healthy volunteers. One study found that in participants (n=14) ≥55 years old, baseline HRV as assessed by the LF/HF power ratio, predicted the response to taVNS applied to the tragus (pulse width 200 µs, frequency 30Hz, 15 minute duration) [60]. In a follow-up including 49 participants (≥55 years old), various measures of HRV, including RMSSD, pRR50, SD1, and HF power were increased, where again the response could be predicted by the degree of basal sympathetic tone/autonomic imbalance.

Vagus somatosensory evoked potentials (VSEP): These evoked field potentials are a potential non-invasive way to measure vagus nerve function [56]. Far-field potentials are recorded by electrodes placed on the scalp (C3–F3, C4–F4, Fz–F3, Fz–F4) following stimulation of the vagus nerve, typically the auricular or cervical branch, and used as a surrogate for evoked potentials occurring in vagus nerve nuclei in the brainstem. While some studies have found that VSEPs can be evoked by tVNS, the effect is not reliable across study participants [56]. A systematic review of studies examining VSEPs found that responses showed high variability, low validity, and poor reproducibility [61]. Additionally, VSEP latencies were not reliable biomarkers of neurological and neurodegenerative conditions. While some components of the VSEP response may be vagally mediated, others components appear to be derived from neuromuscular activity [56]. Therefore, VSEPs may not be good indicators of vagus nerve activity.

Pupil dilation: The activity of the pupil dilator and sphincter muscles is influenced by the locus coeruleus-noradrenergic system [56]. Measures of pupil diameter can provide an indication of baseline arousal, which is influenced by the activity of the locus coeruleus-noradrenergic system. However, the relationship is complex, as it can also be influenced by other neurotransmitter systems. Three studies assessing tonic pupil diameter found that there was no effect following taVNS using the left cymba concha stimulation site [56]. One of these studies found that taVNS did impact phasic pupil diameter. A study comparing the tragus and cymba conchae sites found that taVNS did not significantly affect pupil diameter for either site. These studies suggest that pupil dilation is not a reliable biomarker for tVNS.

Salivary alpha-amylase: This protein is considered a marker of sympathetic nervous system activity, however, levels are affected by the combined activity of the sympathetic and parasympathetic nervous system [56]. Since the parasympathetic nervous system also influences salivary flow rate, salivary alpha-amylase levels need to be considered with respect to salivary flow rate. Some tVNS studies have shown an increase in salivary alpha-amylase levels following stimulation, however, technical concerns regarding the collection procedures and analysis raise concerns regarding the reliability and potential reproducibility of these findings.

Safety: tVNS is generally considered safe for people without cardiac abnormalities, with stimulation site irritation as the most common side effect. Further studies aimed at optimizing stimulation parameters are needed.

Types of evidence:

- 1 systematic review of safety in tVNS studies
- 1 systematic review of tVNS/VNS studies for postoperative complications
- 1 systematic review of VNS studies for stroke rehabilitation
- 1 systematic review of VNS studies assessing cognition
- 1 review of VNS for epilepsy
- 1 safety review of VNS complications
- 6 reviews of VNS/tVNS stimulation parameters
- 1 review of tVNS for tinnitus
- 5 clinical studies testing tVNS
- 2 clinical studies testing VNS in Alzheimer's disease
- 1 clinical trial of VNS for heart failure
- Numerous laboratory studies

All forms of VNS are generally safe and well-tolerated, although the adverse event profile differs between invasive and non-invasive (i.e. transcutaneous) forms of VNS, due to the surgical implantation procedure. A safety review of surgical and hardware complications for 497 procedures performed for 247 primary VNS implant procedures over a 25-year period found a surgical complication rate of 8.6%, and a hardware complication rate of 3.7% [62]. The most common surgical complications were infection (2.6%), postoperative hematoma (1.9%), and vocal cord palsy (1.4%). Vocal hoarseness tends to be the most common adverse event for invasive VNS, due to the location of the implantation. A 30-year review

of VNS for epilepsy found that most adverse events are related to the surgery, and that other effects tend to be intermittent and most prominent during the stimulation phase, with voice hoarseness being the most common (38.8 %) [63]. Other adverse events tended to occur at rates of 5% or less, including dysphonia, cervical pain, exertional dyspnea, cough, and snoring. In a systematic review of seven RCTs (n=236 patients) using VNS for stroke rehabilitation, the most common adverse events were post-operative pain, followed by hoarseness, coughing, headache, and wound infection [42]. Similarly, in pilot VNS studies in AD patients, the most common adverse event was vocal hoarseness, followed by cough, pain, dysphagia, hematoma, itch, dizziness, and lead site inflammation [24; 25]. VNS does not appear to negatively impact cognitive function [6].

The side effect profile for non-invasive tVNS is considerably milder [63]. A systematic review of 51 tVNS studies including 1,322 participants found that the most common adverse events were local skin irritation from electrode placement in 240 participants (18.2%), headache in 47 participants (3.6%) and nasopharyngitis in 23 participants (1.7%) [64]. Other reported side effects were dizziness, facial droop, nausea, and pain distal to the stimulation site. Only three serious adverse events were deemed to be potentially related to tVNS, and include heart palpitations, vestibular neuronitis (vertigo), and a skin lesion. In the majority of tVNS studies, pain or tingling at the stimulation site is the primary or only adverse event [37; 49; 55]. A review of tinnitus studies suggests that use of tVNS for up to six months, appears to be safe and well-tolerated [45]. The safety profile for long-term chronic tVNS has not been established, as most studies are short in duration, but is expected to be as good or better than that for invasive VNS [63].

The primary potential concern for VNS relates to its ability to impact cardiac function. Cardiomotor efferent vagal nerve fibers innervate cardiac tissue and modulate activity through the sinus node, which affects heart rate [65]. Sensory afferent fibers can also affect cardiac activity via regulation of the autonomic nervous system. There is an asymmetry to the vagus nerve, including a right-side dominance for cardiac innervation, with the right vagus nerve predominately innervating the pace-making sinoatrial node [2]. Studies in dogs found that right side VNS could induce bradycardia, which led to the near exclusive use of left side implantation for invasive VNS [2]. However, the degree of asymmetry and structure of the cervical vagus trunk differs across species, such that the cervical electrode site in humans does not impact the cardiac branches the way it does in dogs [2]. Chronic VNS has been shown to be safe in patients with heart failure, with the safety profile comparable to the use of VNS in other populations [66; 67].

Since tVNS generally only activates afferent fibers, it poses a lower risk for adverse cardiac effects [55]. There does not appear to be a similar requirement for left side stimulation with tVNS as both right and

left side tVNS have safely been used, although as a precaution, the majority of tVNS studies have used exclusively left side stimulation. In a review of tVNS studies, five studies reported cardiac side effects (from seven participants) including palpitations, arrhythmia, hypotension and bradycardia [64]. With the exception of one participant being subjected to a painful stimulus during bilateral conchal tVNS, the other reported cases of tVNS-related heart rate reduction were asymptomatic. Cardiac arrhythmias were reported in two patients undergoing tVNS for tinnitus [68]. These effects were deemed incidental, however, there was a tendency for the tVNS to reduce the QRS complex duration on ECG in these subjects. Although rare, ECG monitoring may be useful upon initiation of tVNS to assess the potential for bradycardia or arrhythmia.

Drug interactions: Due to the requirement for left side implantation, invasive VNS is contraindicated in individuals with left side vagotomy [67]. Patients with implanted VNS also need to be careful around machines which induce strong electrical or magnetic fields, such as MRI or ultrasound machines, as they can interfere with the function of the VNS [63].

tVNS is not currently approved for use in pregnant women, patients with implanted medical devices, patients with cardiac (ECG) abnormalities, as well as other high risk groups such as cancer patients or those with head trauma (gammaCore® instructions).

One study found that patients taking beta blockers were less responsive to tVNS [15].

Sources and dosing:

DEVICES

The gammaCore Sapphire™ is the only FDA approved tcVNS device, with clearance for the treatment and prevention of migraine and cluster headache, and is available with a doctor's authorization. The device uses a stimulation paradigm with a 5 kHz sine wave burst for 1 ms, delivered at a 25Hz frequency, with a 24V peak voltage and 60mA peak output current that is modulated to tolerability. The recommended dosage is three consecutive two minute stimulations either daily, within one hour of waking (for prevention), or at the onset of headache symptoms (treatment) (gammaCore® instructions).

The tVNS® L (formerly NEMOS®) taVNS device has the CE mark for the treatment of epilepsy, depression, and migraine pain, and is available in Europe with a doctor's authorization. A research use version, tVNS® R is also available for clinical research studies. It is a taVNS device with stimulation at the left cymba concha.

The ParaSymp™ device from ParaSymp Ltd is a class IIa medical device with the CE mark and is available for use in qualified patients in the UK and EU. It is a taVNS device with stimulation at the tragus. It is

currently only available for research use in the US, and has been designated Non-significant Risk and given an Investigational Device Exemption for several indications by the FDA.
Clinical research use taVNS devices are also available through Soterix Medical.
tVNS devices for general health and wellness, which have not been approved for any specific indication, are also commercially available. Although not yet available, the Bodus™ earbud neurostimulator from XANA™, activates the auricular branch of the vagus nerve and has undergone some clinical testing. The company is also developing a bilateral vagus nerve stimulator called DEVA, as well as a vagus nerve stimulator for cardiological conditions called HATY (https://xanastim.com/medical-pipeline).

STIMULATION PARAMETERS
VNS: The stimulation settings should be tailored to the indication and the individual [69]. The most commonly used VNS protocol for epilepsy is a 500 µs pulse width, 30Hz frequency, with cycling 30 seconds on and 5 minutes off [7]. For depression, it is most commonly a 500 µs pulse width, 20Hz frequency, with cycling 30 seconds on and 5 minutes off. Neurorehabilitation studies tend use a 100 µs pulse width, 30Hz frequency, delivered in a 500 ms train at a current intensity of 0.8mA, which is paired with training.

tVNS: The stimulation parameters used in tVNS are typically based off of what has been used with invasive VNS. tVNS protocols typically use frequencies between 20 and 30Hz, a pulse width of 250 or 500 µs, and a current intensity to tolerability [70]. The optimal length of stimulation has not been established. tcVNS protocols, particularly those using the gammaCore® device, typically use two-minute stimulation periods [2]. The optimal number of these sessions is unclear, and may vary based on individual characteristics and/or indication [2; 71]. taVNS protocols typically stimulate for periods of 30 to 60 minutes, but again may vary depending on the desired outcome measures. The durability of the effects of tVNS has not been established, so it is currently unclear for most conditions how long treatment is needed to induce an effect and the frequency needed to maintain the effects [2]. The type of waveform (monophasic or biphasic) is determined by the type of device used, and could potentially play a role in outcomes, although no systematic comparison has been done [2]. While most studies use a monophasic (square) waveform, there is some evidence that the use of a biphasic rectangular waveform may help prevent irritation at the stimulation site [69]. For implanted VNS devices, frequencies greater than 50Hz have the potential to cause damage, which is why stimulation is generally done at frequencies between 20-30Hz [65]. However, the safety threshold for tVNS may be different, such that the 20-30Hz frequency range typically used, is not necessarily optimal for tVNS, depending on the indication. Indeed, one study found that a 10Hz frequency, combined with a 500 µs pulse width, had the strongest effect on

heart rate [7]. There appears to be an interaction between current intensity and pulse width, such that stronger effects are seen with larger pulse widths at a given current intensity, but high current intensities may only be tolerable at low pulse widths [49]. Additionally, variation in skin impedance, due to differences in skin thickness and sweat glands, can affect pulse shape and current [69]. The current intensity determines the degree of vagal nerve fiber activation. The vagus nerve is a bundle containing thousands of nerve fibers each with their own activation threshold, some of which require higher intensities to activate than others. In tVNS studies, current intensity is typically calibrated to tolerability, which means to the degree of sensation (tingling) without causing pain, which generally involves current intensities less than 5mA [70]. The targeted vagal nerve afferents are the thickly myelinated A-beta fibers, so they are more easily activated than the thin or unmyelinated C-fibers, which carry pain information [70]. However, one of the difficulties of tVNS is that individual differences in nerve anatomy can influence the degree of vagal nerve activation at particular electrode sites, which can impact differences in tolerability and efficacy.

There is currently no consensus on the optimal electrode site for tVNS [69]. The cervical branch of the vagus nerve contains five to six times more A-beta fibers relative to the auricular branch, suggesting that tcVNS would allow for more robust vagal nerve stimulation [2]. However, there is a lot of heterogeneity across individuals, which may account for the lack of efficacy in some people. With respect to taVNS, studies have shown effects with stimulation at both the tragus and the cymba conchae. The cymba tends to be the preferred site because it is expected to be fully innervated by the auricular branch of the vagus nerve, while the tragus is only partially (~45%) innervated by it [72]. However, due to differences in anatomy, some people may have a higher degree of tragus innervation. Additionally, the tragus is easier to access, allowing for proper placement, and some studies suggest better tolerability at higher current intensities, thus allowing for greater nerve fiber activation [22]. The use of the earlobe as a sham site has complicated many taVNS studies, because earlobe stimulation activates the auricular branches of other cranial nerves and depending on one's anatomy could potentially influence vagal activity [22].

Research underway:

According to Clinicaltrials.gov, there are currently at least 80 active clinical trials using VNS, inducing at least 50 trials for tVNS. These include trials for non-invasive tVNS for mild cognitive impairment, kidney disease, diabetic neuropathy, long covid, post-traumatic stress disorder, lupus, neurorehabilitation, alcohol withdrawal, rheumatoid arthritis, depression, anxiety, gastroparesis, epilepsy, osteoarthritis, POTS, obesity, tinnitus, as well as other conditions.

Search terms:

Pubmed, Google: VNS, tVNS, tcVNS, taVNS

- Alzheimer's disease, cognition, inflammation, aging, clinical trials, systematic review, meta-analysis, safety, biomarkers, stimulation parameters

Websites visited for Vagal nerve stimulation:

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