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NEUROMODULATION (M GOFELD, SECTION EDITOR)

Review of the Uses of Vagal Nerve Stimulation in Chronic Pain Management

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Abstract Recent human and animal studies provide growing evidence that vagal nerve stimulation (VNS) can deliver strong analgesic effects in addition to providing therapeutic efficacy in the treatment of refractory epilepsy and depression. Analgesia is potentially mediated by vagal afferents that inhibit spinal nociceptive reflexes and transmission and have strong anti-inflammatory properties. The purpose of this review is to provide pain practitioners with an overview of VNS technology and limitations. It specifically focuses on clinical indications of VNS for various chronic pain syndromes, including fibromyalgia, pelvic pain, and headaches. We also present potential mechanisms for VNS modulation of chronic pain by reviewing both animal and human studies.

Keywords Vagal nerve stimulation · Chronic pain · Headache · Inflammation · Pelvic pain · Fibromyalgia

Introduction

Over the last two decades, evolving animal and clinical data have suggested that under certain defined parameters (i.e., output current, frequency, pulse width, and stimulation on-and-off time), vagal afferent stimulation possesses analgesic potential [1, 2]. With the recent development of implantable and portable vagus nerve stimulators, growing evidence suggests that vagal nerve stimulation (VNS) can be used to modulate nociception, and potentially for other clinical indications, in addition to its current use for refractory epilepsy and depression [3–7]. In addition to implantable vagus nerve stimulators, which pose a risk for adverse events from infection and potential cardiac events, newer generation noninvasive stimulators are available that provide a better balance between efficacy and tolerability [8••].

We present an updated review of the studies supporting the use of VNS as a chronic pain treatment modality and stratify it based on clinical indication. We also survey current invasive and noninvasive VNS devices on the market, with specific focus on pertinent intraoperative and postoperative complications. In addition, based on animal and clinical studies, we review and propose potential mechanisms by which VNS might modulate nociception, such as through various signaling and inflammatory pathways. Though VNS devices are not commonly used in chronic pain centers, the data suggest that the technology has tremendous potential to be incorporated into our chronic pain armamentarium and may serve as an additional alternative to reduce opioid use in various chronic pain disease states.

Role of the Vagus Nerve

The vagus nerve possesses 20 % efferent and 80 % afferent sensory fibers that are important in relaying visceral, somatic, and taste sensations [9–11]. The vagal nerve pathway starts in the thoracic and visceral abdominal organs, passes though the nucleus tractus solitarius, and terminates in higher cerebral centers that include the locus ceruleus, dorsal motor nucleus of the vagus, medulla,

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amygdala, hypothalamus, parabrachial nucleus, and the thalamus [12–14]. The locus ceruleus is a major component of VNS-induced release of norepinephrine, a key neurotransmitter that controls seizure threshold and plays a critical role in mood regulation [15]. The vagus nerve also contains parasympathetic efferents that innervate the heart, lungs, and gastrointestinal tract. The right vagus nerve is responsible for innervating the sinoatrial node, and the left vagus nerve innervates the atrioventricular node. These innervations are key anatomical considerations during placement of VNS electrodes [16]. To avoid potential bradycardia, VNS electrodes are placed on the left vagus nerve above the aortic arch and associated subclavian and carotid branches. Even with this approach, occasional retrograde stimulation can result in bradycardia and arrhythmias commonly observed during intraoperative placement of the device [17]. Similar retrograde stimulation of the recurrent and superior laryngeal branches of the vagus nerve during intraoperative device placement can result in voice alteration and frequent hoarseness in patients due to the vagus nerve providing motor and sensory innervation to the pharynx and larynx. The vagus nerve connections are important to our understanding of how stimulation leads to modulation of seizure threshold, mood, and potentially analgesia, but they also explain potential adverse events encountered by practitioners when using VNS in their patients. Comprehensive reviews on the anatomy and function of the vagus nerve can be found for the readers' benefit [18, 19, 20••].

Device Placement

The VNS device is placed in the neck with an electrode targeting the left vagus nerve. Additionally, a pulse generator/stimulator is implanted in the anterior chest wall subcutaneously or subpectorally [21]. The pulse generator has defined programmable parameters of frequency, output current, pulse width, and stimulation ON-time and OFF-time determined by the physician and patient. Physicians typically conduct impedance testing with an output current of 1 mA, pulse width of 500 ms for duration of 60 s, and stimulus of 20 Hz, while monitoring vital signs in the operating room. The device is typically activated 2 to 3 weeks post-implantation in the clinic [20••, 22, 23]. VNS devices do not usually monitor peripheral and central nervous system activity; therefore, a pulse magnet must often be placed over the pulse generator for activation [24]. It is important to note that placing the magnet for more than 65 s typically causes inactivation of the device [20••].

Implantable and Noninvasive VNS Devices

Implantable VNS Devices

By August 2014, 100,000 VNS devices had been implanted in 75,000 patients worldwide [25]. Figure 1a and b shows images of the latest implantable VNS devices. Studies indicate that a quarter to half of patients achieve more than 50 % seizure reduction with VNS [23, 26, 27]. Therefore, VNS therapy was approved for epilepsy treatment by 1997 in both the USA and Europe. Based on observable mood improvements in patients who were being treated for epilepsy with implantable VNS, in 2005, the United States Food and Drug Administration approved the use of implantable VNS for refractory depression in patients 18 years or older who were unresponsive to four or more antidepressants [28–30]. Other indications for implantable VNS include refractory migraines, cluster headaches, heart failure, Alzheimer's disease, anxiety, and obesity [31–37]. The major issues facing use of VNS therapies remain safety and tolerability. The most frequent surgical complications include bradycardia, vocal cord paresis, asystole, infections, and lower facial weakness [38]. The incidences of these adverse events are reduced in patients with continued treatment. Cardiac adverse events during the intraoperative and initial device testing include bradycardia, ventricular asystole, and complete heart block [39–42]. There has been no indication of teratogenicity in pregnant patients with the device [43, 44]. Positive improvement in mood, alertness, memory, and thinking has been reported with minimal central

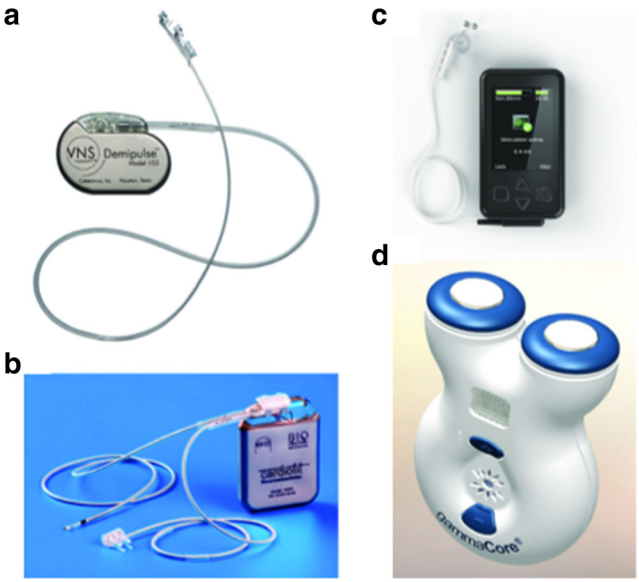

Fig. 1 **a** Implantable VNS systems: VNS Therapy system reprinted with permission from Cyberonics, Houston, TX, USA. **b** CardioFit reprinted with permission from BioControl Medical, Yehud, Israel. **c** Non-implantable VNS systems: NEMOS (tVNS) reprinted with permission from Cerbomed, Erlangen, Germany. **d** GammaCore (nVNS) reprinted with permission from electroCore, Basking Ridge, NJ, USA. The following images were obtained and reprinted with permission from [8••]

nervous system side effects. Currently, CardioFit (BioControl Medical Ltd., Yehud, Israel) is being trialed for heart failure treatment, as it has specifically shown improvement in NYHA II-III heart failure. No serious adverse events were reported and most side effects resolved with ongoing treatment [33, 45].

Noninvasive VNS Devices

Several noninvasive VNS (nVNS) devices are currently on the market, as shown in Fig. 1c and d. NEMOS (Cerbomed, Erlangen, Germany) provides transcutaneous VNS via the auricular branch of the vagus nerve [46]. The patient controls the stimulation intensity and duration of treatment. Busch et al. showed that the NEMOS device increased mechanical and pressure pain thresholds and lowered pain ratings to painful heat compared with sham treatment [47]. No clinically relevant cardiovascular or other adverse events were reported with this form of VNS. GammaCore (electroCore LLC, Basking Ridge, NJ, USA), an alternate transcutaneous device that delivers a proprietary low-voltage electrical signal via the cervical vagus nerve with stimulation cycles that last 120 s, is currently being tested for headache, epilepsy, and gastrointestinal disorders [48]. Its primary use has been for cluster headaches, episodic migraines, and chronic migraines. Reportable adverse events across several published studies include local discomfort, skin irritation, transient muscle stiffness, and pain that resolved with NSAID treatment [49–52].

Summary of Complications from VNS Devices

Intraoperative Complications

Ardesch et al. reported that three of 111 patients who received VNS device placement experienced bradycardia resulting from VNS retrograde stimulation of the sinoatrial node. This effect occurred most commonly during lead impedance testing [41]. Unilateral vocal cord dysfunction and immobile vocal cord in the paramedian position have been reported during the dissection phase of the surgery secondary to nerve trauma, predisposing patients to increased risk of postoperative aspiration [53]. In addition, risks of peritracheal hematoma can contribute to hoarseness, dyspnea, and voice alteration owing to emergent surgical wound exploration and hematoma evacuation. Delayed arrhythmias inclusive of second degree heart blocks and asystole have been reported in pediatric and adult patients, but these resolved on device removal [54, 55].

Postoperative Complications

Voice alterations, which occur with an incidence of 66 %, are commonly dependent on the frequency of VNS. Frequencies higher than 40 Hz simulation lead to an increased incidence of vocal cord adduction and hemispasms [56, 57]. Vocal cord paralysis can also occur during high output VNS as a result of vagus nerve inflammation, surgical trauma, or reaction to the original implantation, increasing risk of aspiration as reported in several studies [53, 58, 59]. Studies have also shown in both adult and pediatric populations that VNS during sleep can alter tidal volumes and respiratory rate, increasing the incidence of obstructive sleep apnea with increased apnea-hypopnea index (AHI) post-stimulation. These symptoms seem to resolve with use of continuous positive airway pressure (CPAP) [60–62]. Recommendations for physicians include noninvasive positive pressure ventilation as required, routine monitoring of sleep-disordered breathing preoperatively and postoperatively, prolonging OFF-time parameters, and minimizing stimulation frequencies [60, 63, 64].

Other key considerations include using bipolar rather than monopolar electrocautery to reduce the risk of damage to the device. MRI body imaging is also not recommended for patients who have implantable VNS devices, as heat can cause thermal injury to the vagus nerve, surrounding structures, and the device itself. It is advisable that after any surgical procedure or MRI, the physician should have a low threshold to interrogate and reprogram the device for maximal utility if the device is turned off to accommodate the procedure.

Clinical Studies and Indications for the Use of VNS for Chronic Pain Pathologies

In addition to the increasing use of VNS for treatment of medication-resistant epilepsy and depression, there is a limited but growing body of literature supporting its use for multiple pain indications. Among these indications are chronic pelvic pain, fibromyalgia, trigeminal allodynia, and chronic headaches and migraines.

Trigeminal Allodynia

In a 2014 paper, Oshinsky et al. demonstrated the potential utility of VNS for treatment of trigeminal allodynia in a rat model. The researchers showed that periorbital sensitivity in allodynic rats decreased for up to 3.5 h after 2 min of nVNS. They also showed that the amount of extracellular glutamate, a neurotransmitter that increases with painful stimuli, decreased in the trigeminal nuclei caudalis of allodynic rats treated with nVNS after a chemical vasodilatory headache trigger, compared to that in rats without nVNS. These findings suggest not only that nVNS may be useful for treating trigeminal allodynia but also that the pain relief is achieved through suppression of glutamate after a vasodilatory trigger, in this case nitric oxide [65].

Fibromyalgia

In a small phase I/II proof-of-concept trial (n=14), Lange et al. examined the safety and tolerability of VNS in treatment-resistant fibromyalgia and determined preliminary measures of efficacy as a secondary endpoint in this small cohort [66]. They concluded that the side effects and tolerability of VNS for treatment-resistant fibromyalgia were largely similar to those reported with other disorders currently treated with VNS, including medication-resistant epilepsy and depression. They also noted an improvement in tender point threshold and number in some of their subjects, with five patients no longer fulfilling either the widespread pain criteria or the tender point criterion for fibromyalgia at the 11-month follow-up. These findings suggest that VNS may potentially decrease, or tune down, the pathophysiologic processes involved in the central sensitization seen in fibromyalgia. This action may be the mechanism by which VNS reduces the widespread musculoskeletal pain seen in fibromyalgia and comparable pathologies [66].

Chronic Pelvic Pain

VNS has also been considered for treatment of patients with chronic pelvic pain. In a small study (n=15), researchers examined the efficacy of a more targeted type of VNS called respiratory-gated auricular vagal afferent nerve stimulation (RAVANS), hoping that they could further optimize pain relief with nVNS, given that the dorsal medullary vagal system operates in concert with respirations. In this randomized, crossover pilot study, researchers compared RAVANS to an active control consisting of non-vagal auricular nerve stimulation. They found that chronic pelvic pain patients treated with the more targeted RAVANS had significantly less anxiety than those treated with nonvagal auricular stimulation. They also saw a trend toward reduced evoked pain intensity and temporal summation of mechanical pain with the more targeted stimulation. Together with what is already known about VNS and its anti-nociceptive and anti-inflammatory effects, findings from this and similar studies demonstrate promise in terms of addressing the hyperalgesia and central sensitization associated with chronic pelvic pain and other chronic pain syndromes [67].

Headache

Current evidence for the use of VNS for pain indications is most robust, though still relatively limited, for the indication of chronic headaches and migraines. In a recent single-arm, open-label study, patients with high-frequency episodic migraines and chronic migraines self-treated up to three consecutive mild or moderate migraine attacks that occurred during the 2-week trial with two 120-s doses of nVNS to the right cervical branch of the vagus nerve (cervical nVNS). The study found that the majority of patients (56.3 %, n=27 at 1 h and 64.6 %, n=31 at 2 h) reported pain relief, defined as a ≥50 % reduction in pain on the visual analog scale. Of these patients, 35.4 % (n=17) reported being pain-free at 1 h, and 39.6 % (n=19) reported pain-free status at 2 h [68]. Another study found more modest benefit with two 90-s doses of nVNS to the same branch of the vagus nerve, with 47 % (n=9) of participants experiencing pain relief after 2 h of treatment and 21 % (n=4) reporting pain-free status at 2 h after nVNS treatment. It is important to note that although no unanticipated or serious adverse events were reported, some mild to moderate adverse effects were noted in a minority of study participants, including raspy voice, neck twitching, and redness at the site of stimulator application (all n=1) [51]. Together, these observational studies suggest a useful role for nVNS in the treatment of acute migraine. Most recently, a randomized controlled trial conducted in Germany by Straube et al. showed that, compared to an active control group, chronic headache patients who used nVNS for 4 h/day had a significantly larger reduction in headaches by the end of the 3-month trial. Pain relief was reported in 29.4 % of the treatment group compared to only 13.3 % in the active control group. Additionally, the nVNS treatment group had a significantly larger reduction in headache days per 28 days than did the control group (−7.0± 4.6 vs. −3.3±5.4 days, p=0.035) [69].

Additional Studies

Busch et al. conducted a randomized, double-blind controlled crossover study in 48 healthy volunteers in which they examined the effect of transcutaneous VNS in the left ear on pain perception. They found in the ipsilateral and contralateral hand an increase in mechanical and pressure pain thresholds and through quantitative somatosensory testing a reduction in mechanical pain sensitivity. With mean current intensities of 1.6 mA, the investigators found no serious adverse events in the treatment group [47].

Table 1 provides a summary of different studies, stimulation schedules and device parameters, efficacies, and potential adverse effects reported by the various studies described above that have addressed the use of VNS for chronic pain pathologies.

Proposed Mechanisms by Which VNS Modulates Chronic Pain

Though the exact mechanisms by which VNS modulates chronic pain remain to be elucidated, investigators have proposed several hypotheses based on animal and clinical observations. It has been shown that VNS inhibits spinal cord neurons below level C3 but excites neurons between C1 and C3.

Table 1 Summary of studies

Study (lead author, year)	Indication	Model and sample size[a]	Study design	Stimulation schedule and device parameters	Efficacy	Adverse events
Lange 2011 [66]	Fibromyalgia	Human, $n=14$	Open-label longitudinal study	3-month "acute study" with follow-up at 5, 8, and 11 months after stimulation initiation. Patients received 250 μS 20 Hz pulses with 30 s ON and 5 min OFF. Current intensity: 0.75–2 mA (median 1.5 mA)	At 3 months, 5 pts had attained efficacy criteria with, 2 no longer meeting criteria for widespread pain or tenderness criteria for fibromyalgia. At 11 months, 7 pts had attained efficacy criteria, with 5 no longer meeting criteria for widespread pain or tenderness criteria for fibromyalgia	Similar AEs to iNVS in refractory depression and epilepsy but also with stimulus-bound electric-like sensation across chest and left arm, which decreased with lowered VNS intensity ($n=1$), dry mouth, and increased fatigue ($n=3$); rates of neck/facial pain,headaches, and dyspnea were higher than in refractory MDD and epilepsy
Napadow 2012 [67]	Pelvic pain	Human, $n=18$	Counterbalanced crossover study	Patients in treatment group completed two 30-min experimental sessions, spaced at least 1 week apart. 450-μS pulses of 30 Hz for 0.5 s, gated to the expiratory phase of respiration	Those in the treatment arm showed a trend for reduced pain intensity and temporal summation of pain, and had a significant reduction in anxiety compared to controls	None noted
Oshinsky, 2014 [65]	Trigeminal allodynia	Rat, $n=15$	In vivo study with appropriate controls and treatment groups	Rats received 2 min of repeated 25 Hz 1-ms pulses. The effect of nVNS was compared in allodynic and naïve rats and later in allodynic rats that received a vasodilatory headache trigger	Allodynic rats showed a decrease in periorbital sensitivity for up to 3.5 h after 2 min of stimulation. Allodynic rats that received nVNS after a chemical vasodilatory headache trigger showed a quantitative decrease in the amount of extracellular glutamate in the trigeminal nuclei caudalis compared with that of controls	None noted
Barbanti et al. 2015 [68]	Chronic migraine	Human, $n=50$	Open-label single-arm, multiple attack study	Patients self-administered two 120-s doses of nVNS at 3-min intervals to the right cervical branch of the vagus nerve for migraine pain over the course of 2 weeks	Most patients (56.3 % at 1 h and 64.6 % at 2 h poststimulation) reported pain relief, defined as a ≥50 % reduction in visual analog scale. Of these patients, 35.4 and 39.6 % reported pain-free status at 1 and 2 h, respectively	No major adverse events; mild tingling or prickling sensations at the stimulation site ($n=32$)
Goadsby 2014 [51]	Acute migraine	Human, $n=30$	Open-label single -arm, multiple attack study	Patients self-administered two 90-s doses of nVNS at 15-min intervals to the right cervical branch of the vagus for acute migraine attacks over the course of 6 weeks	47 % patients had pain relief after 2 h of treatment, and 21 % reported pain-free status at 2 h post-nVNS treatment	No serious or severe adverse events were reported; mild-moderate adverse events were reported

Table 1 (continued)

Study (lead author, year)	Indication	Model and sample size[a]	Study design	Stimulation schedule and device parameters	Efficacy	Adverse events
						in 13 pts, including raspy voice, neck twitching, stiff neck, dizziness, tinnitus, and site redness
Straube 2015 [69]	Chronic migraine	Human, n=46	Double-blind RCT	Patients were randomized to receive either 25 Hz (active control) or 1 Hz (treatment) nVNS at the sensory vagal area by the left ear for 4 h each day for 3 months	Pain relief was reported in 29.4 % of the treatment group but in only 13.3 % of the active control group. The reduction in headache days per 28 days was significantly larger in the treatment group than in the control group	No serious or severe treatment-related adverse events were reported; the most frequent treatment-related adverse events included problems at the stimulation site, such as erythema, pruritus, paresthesia, mild-moderate pain ulcer, or scab
Busch 2013 [47]	Healthy volunteers	Human, n=48	Double-blind RCT, crossover study	Patients participated in two experimental sessions with active nVNS or sham nVNS on different days in a randomized order (crossed-over). One session consisted of two QST measurements on the ipsilateral and contralateral hand, each before and during 1 h of a continuous nVNS on the left ear using rectangular pulses (250 μS, 25 Hz)	Patients in the stimulation group noted an increase ofmechanical and pressure pain threshold and a reduction in mechanical pain sensitivity compared to those in the sham group. Active nVNS significantly reduced pain ratings during 5-min sustained application of painful heat. No relevant alterations of cardiac or breathing activity or clinically relevant side effects were observed during nVNS	No relevant alterations of cardiac or breathing activity or clinically relevant side effects were observed during t-VNS

[a] Device was implanted only in the study by Lange. It was used noninvasively in all other studies

RCT randomized controlled study

This mechanism would suggest that propriospinal neurons from high cervical segments may play a critical role in vagally mediated antinociception [70–72]. Studies in a rat model have suggested that lower stimulation intensities of 20 to 50 μA have a facilitatory effect on pain behavior, whereas higher stimulation intensities above 50 μA have an inhibitory effect. This biphasic pattern could be induced by stimulation of cervical, cardiac, or thoracic vagal afferents that inhibit second-order nociceptive neurons in the spinothalamic and spinoreticular tracts [73–77]. Subsequent animal work, in which neonatal rats were treated with capsaicin to deplete C-fibers of substance P and calcitonin gene-related peptide within the nucleus tractus solitarius, suggested a role for C-fiber activation in VNS pain reduction [2]. Whether these findings are germane to humans is not quite clear, as the duration of VNS is much longer in humans. However, Ness et al. suggested that some parallel mechanisms were in play in their clinical study [5]. In addition, key structures identified through local anesthetic studies, including the nucleus tractus solitarius, raphe magnus, locus ceruleus, and periaqueductal gray, may play an important role in VNS modulation of pain [78–81]. Based on positron emission tomography imaging, VNS also seems to affect "pain network" sites, including the thalamus and hypothalamus [82–84]. Growing evidence suggests that levels of specific neurotransmitters such as serotonin, noradrenaline, opioids, and GABA in the cerebrospinal fluid may play a role in modulating mood and chronic pain [75, 85–87]. In addition, indirect activation of the paraventricular nucleus through vagal afferent impulses increased adrenaline release from the adrenal medulla, in conjunction with increased plasma ACTH and corticosterone. These increases might mediate antinociceptive and anti-inflammatory effects [88, 89].

Interestingly, in a recently published article in *Scientific American*, Tracey suggested that VNS may have tremendous potential in dampening host inflammation by modulating the proximal inflammatory cytokine TNF-alpha. TNF downregulation, the author suggests, may play a key role in how VNS might modify and reduce chronic pain in various disease pathologies [90].

Conclusion

Though the science of VNS is still in its infancy, VNS therapy has potential for use in the treatment of various chronic pain states. At present, no clearly defined mechanism has been elucidated in regard to how VNS modulates chronic pain. However, increasing evidence points to anti-inflammatory effects working in conjunction with both central and peripheral pain pathways. As increasing evidence emerges from ongoing clinical studies for the use of VNS as a treatment modality for chronic pain, specific focus will have to be placed on the ability to adjust parameters in relation to specific chronic pain endpoints.

Compliance with Ethics Guidelines

Conflict of Interest Krishnan Chakravarthy, Hira Chaudhry, and Paul J. Christo declare that they have no conflict of interest.

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