Vagus nerve stimulation in clinical practice

The diverse array of end organ innervations of the vagus nerve, coupled with increased basic science evidence, has led to vagus nerve stimulation becoming a management option in a number of clinical disorders. This review discusses methods of electrically stimulating the vagus nerve and its current and potential clinical uses.

The autonomic nervous system is a complex hierarchically controlled system, providing a neural link between the brain and the body, whose central function is the maintenance of homeostasis. The autonomic nervous system is composed of two broadly opposing branches, the sympathetic and parasympathetic nervous systems. The vagus nerve is the main neural substrate of the parasympathetic nervous system. A relative paucity of vagal activity, frequently coupled with heightened sympathetic nervous system tone, has been implicated in the pathophysiology of a number of disorders including, but not limited to, heart failure, inflammatory bowel disease and chronic pain syndromes (Ghia et al, 2006; De Ferrari et al, 2011; Farmer et al, 2014). Thus efforts to restore this balance using vagus nerve stimulation is of interest as a potential therapeutic intervention (*Figure 1*).

The vagus nerve is the tenth and the longest of the cranial nerves. It courses from the brainstem to the colon, innervating thoracic and abdominal structures, and has both afferent and efferent branches, although the former predominate (c. 80%). Considering its widespread innervation, it is not surprising that the vagus nerve has a diverse array of functions including maintaining homeostasis within the cardiovascular and respiratory system, by influencing heart rate, vascular resistance, respiratory rate and airway calibre. Within the abdominal viscera the vagus nerve also has a number of important functions regulating and modulating inflammation, gastrointestinal motility, gastric acid secretion, satiety, maintenance of the intestinal barrier and visceral pain sensation.

Accumulating evidence posits a key role of the vagus nerve in modulating pain and inflammation in a bidirectional manner through what is termed 'the cholinergic anti-inflammatory pathway' (Bonaz et al, 2013; Goverse et al, 2016). Tumour necrosis factor (TNF) is a key cytokine in the promotion of inflammation. TNF is the target for many clinically efficacious drugs used in the treatment of immune-mediated inflammatory disorders, such as inflammatory bowel disease and rheumatoid arthritis. The cholinergic anti-inflammatory pathway has direct and indirect efferent arms. First, there is a direct effect on peripherally circulating macrophages via the alpha-7-nicotinic receptors, including those in the muscularis mucosae of the gastrointestinal tract (Matteoli et al, 2014), to reduce the release of pro-inflammatory

Figure 1. Sympathovagal imbalance has been implicated in a number of disorders – aiming to restore this balance may exert a therapeutic effect in these disorders.

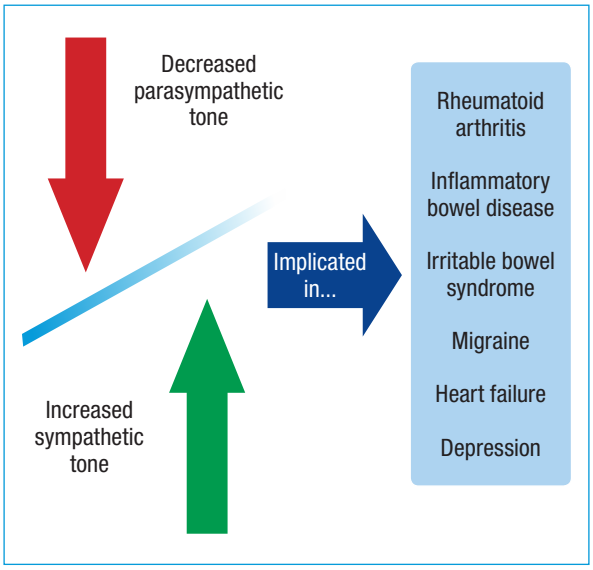

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Figure 2. The cholinergic anti-inflammatory pathway has two efferent arms – indirectly via the coeliac ganglion (CG) to the spleen and also directly via immune cells in the muscularis mucosae in the gastrointestinal tract. Vagus nerve activity has been shown, via the alpha-7-nicotinic receptor expressed on macrophages, to ameliorate pro-inflammatory cytokines. This biological pathway could potentially be harnessed, via vagus nerve stimulation, to result in an anti-inflammatory effect. HMGB1= high mobility group protein box 1; nAChR = nicotinic acetyl choline receptor.

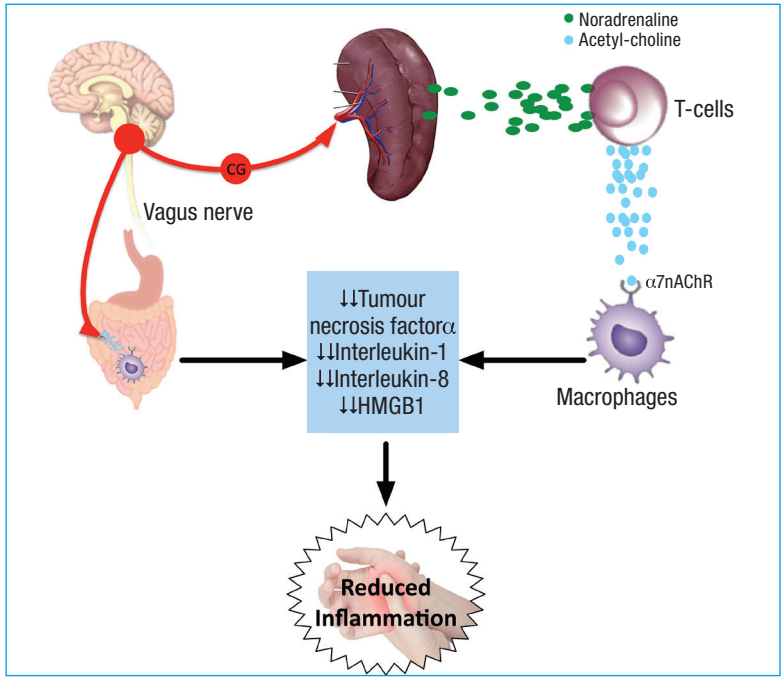
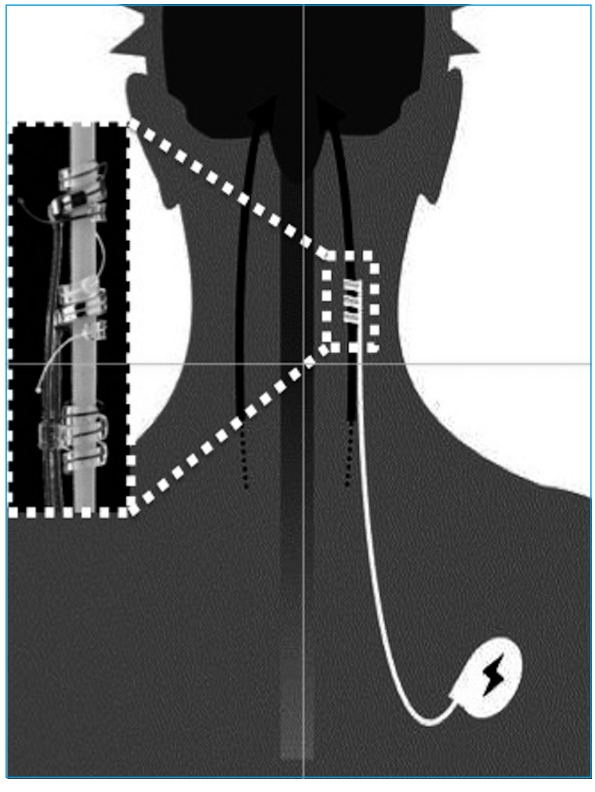


Figure 3. Invasive vagus nerve stimulation. A bipolar helical electrode is surgically implanted around the cervical vagus nerve and attached to a stimulation generator, which is placed in a subcutaneous pocket in the chest.



mediators including TNF-α. Second and indirectly the vagus nerve may mediate the release of acetylcholine at the coeliac ganglion which itself releases noradrenaline. This acts on the spleen to reduce the release of pro-inflammatory cytokines (*Figure 2*). There is also increasing appreciation that this putative pathway may be supplemented by the sympathetic splanchnic anti-inflammatory pathway, driven by the greater splanchnic nerves (Martelli et al, 2016).

This narrative review discusses the methods by which the vagus nerve can be electrically stimulated, the current and potential clinical uses for vagus nerve stimulation and highlights some issues that need to be addressed around these technologies in future clinical trials.

Methods of electrical vagus nerve stimulation

Since 1990 there have been over 5000 published reports concerning vagus nerve stimulation, reflecting the burgeoning field of neuromodulation or 'electroceuticals'. Currently, electrical vagus nerve stimulation can be divided into two groups, namely invasive, or implantable, and non-invasive, or transcutaneous.

Invasive electrical vagus nerve stimulation

Invasive vagus nerve stimulation is most commonly performed as a day case procedure under a general anaesthetic. The left cervical invasive vagus nerve stimulation device (Cyberonics Inc, Houston, Texas, USA) comprises two bipolar helical electrical electrodes (cathodic and anodal) and a securing tether. These are surgically implanted around the left cervical vagus nerve and connected to a stimulating generator most commonly positioned in the left infra-clavicular pocket (Yuan and Silberstein, 2016) (*Figure 3*). The generator delivers low frequency intermittent electrical stimulation to the vagus nerve, although the absolute stimulation parameters can be altered non-invasively using a telemetric device linked to a personal computer. Typical initial stimulation parameters are 0.25 mA (5 minutes off, 30 seconds on with a pulse width of 500 μs, frequency 10 Hz). The amplitude can be increased to 1.25 mA based on patient tolerance (Yamamoto, 2015).

A right cervical invasive vagus nerve stimulation device (CardioFit System, BioControl Medical, Yehud, Israel) has also been developed and in contrast also has a wire that is placed in the apex of the right ventricle which senses the electrocardiogram. This facilitates the delivery of an impulse to the vagus nerve at a predefined delay from the onset of the R wave within the electrocardiogram (Hauptman et al, 2012). The stimulation lead consists of an asymmetrical bipolar multi-contact cuff electrode, designed to cathodically induce action potentials within the vagus nerve while concurrently applying an asymmetrical anodal block, thereby reducing the activation of A-fibres while preferentially stimulating efferent vagal B and C fibres. This design purportedly only stimulates efferent vagal fibres. A further system, consisting of an implantable cervical vagus nerve micro-

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regulator, wireless charger and iPad prescription pad application, is also currently under development (SetPoint Medical, Valencia, California, USA).

Finally, a percutaneous investigational device has been used in research studies, where an electrode is placed through the skin in proximity to the right carotid sheath using ultrasound guidance adopting a sterile technique. The electrode is then attached to an external signal generator, which delivers a specific signal (25 Hz and 0.2 ms pulse width, 1–12volt amplitude) (RPS-1000 Resolve proximity system, ElectroCore LLC, Basking Ridge, NJ, USA).

Side effects of invasive electrical vagus nerve stimulation

Although the global side effects are minimal, several adverse events have been reported with invasive vagus nerve stimulation. There are reports of bradycardia and asystole occurring during intraoperative lead testing, as a result of unintentional direct stimulation of the cardiac branches of the vagus nerve, occurring in approximately 1 in 1000 implantations (Asconape et al, 1999). In the direct postoperative period, implantation can result in a peri-incisional haematoma, dyspnoea and localized infection around the wound site. Up to two thirds of patients experience transient dysphonia with paraesthesia and pain occurring in less than 20% of implantations (Watkins et al, 1995; Malow et al, 2000; Santos, 2003).

It has been assumed that within the neck the vagus nerve runs lateral, and parallel, to the carotid artery with no branching to localized structures in the neck. However, in a human cadaveric study, branching of the cervical vagal nerve was demonstrated in 29% of donors, with the majority of these being unilateral (Hammer et al, 2015). Such branching of the cervical vagus nerve may be partially responsible for side effects such as paraesthesia and dysphonia. Nevertheless, mild transient dysphonia is regarded as a surrogate marker of correct implantation (Yamamoto, 2015). Other evidence suggests that vocal cord dysfunction may occur as a consequence of vagus nerve compression by the stimulation electrode (Santos, 2003). Recent data suggest that the need for repeat surgery is relatively rare with the most common reason being replacement of the stimulator generator reported at a rate of 4–10% over a 6-year follow-up period (Lam et al, 2016).

Cautions with patients with invasive electrical vagus nerve stimulation in situ

Techniques that deliver radiofrequency energy, such as electro-cautery and defibrillation, must be used with caution as they have the potential to preferentially transfer energy through the stimulation wires in the form of heat and cause thermal injury. Magnetic resonance imaging is permitted in patients with an implanted vagus nerve stimulation device, although current recommendations suggest that the strength of the magnetic resonance induction coils should be less than 3 Tesla.

Non-invasive electrical vagus nerve stimulation

To date, two broad types of transcutaneous electrical vagus nerve stimulation have been developed which stimulate either the cervical or the auricular branches of the vagus nerve, thereby obviating the need for surgical implantation. Functional magnetic resonance imaging of the brain has demonstrated that non-invasive vagus nerve stimulation stimulates areas consistent with the contemporaneously accepted understanding of central vagal projections (Frangos et al, 2015). However, one inherent limitation of non-invasive stimulation is patient adherence to treatment regimens, with one study suggesting that only half of patients complied (Jaboli et al, 2014).

Non-invasive cervical vagus nerve stimulation

Transcutaneous cervical vagus nerve stimulation is delivered using a portable handheld device which produces a pulsatile waveform (1 ms pulses comprising 5 Hz sine waves repeated at 25 Hz) which permeates the skin and subcutaneous structures to stimulate the vagus nerve (Gammacore, Electrocore LLC, Basking Ridge, New Jersey, USA) (*Figure 4*). The stimulation is delivered with a fixed dose duration of 2 minutes and can be repeated multiple times per day. The patient can alter the intensity of the stimulus, with the goal being to achieve mild facial twitching thereby suggesting adequate stimulation of the vagus nerve. The absolute frequency of stimulation repetition remains to be determined but some clinical studies have used doses as high as 12 times per day.

Non-invasive auricular vagus nerve stimulation

Transauricular vagus nerve stimulation stimulates the auricular branch of the vagus nerve, also referred to as Arnold's nerve, which supplies the inner aspects of the conchae and cymba conchae, using an electrode which sits adjacent to the nerve (NEMOS, CerboMed, Erlangen, Germany) (*Figure 5*). The electrode is connected to a stimulating box, which delivers biphasic pulses (25 V, 10 Hz, 0.3 ms pulse, 30 seconds stimulation/30 seconds rest), with the amplitude of the pulse being patient modifiable.

Figure 4. Non-invasive cervical vagus nerve stimulation. **a.** This handheld device is placed over the cervical vagus nerve and provides an electrical pulse, which stimulates the nerve. **b.** A subject delivering vagus nerve stimulation.

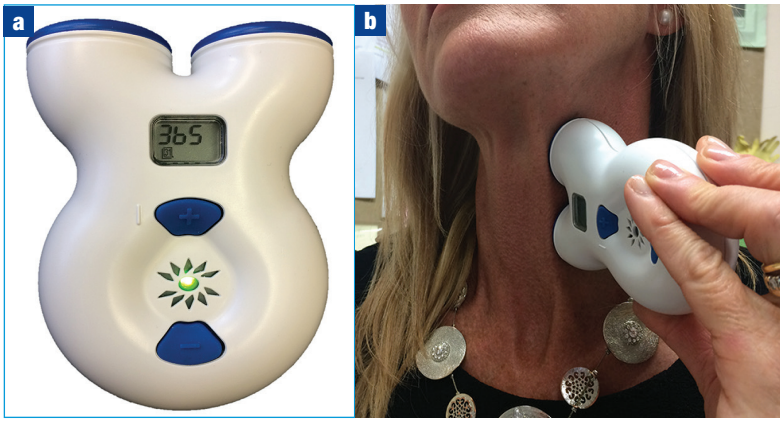

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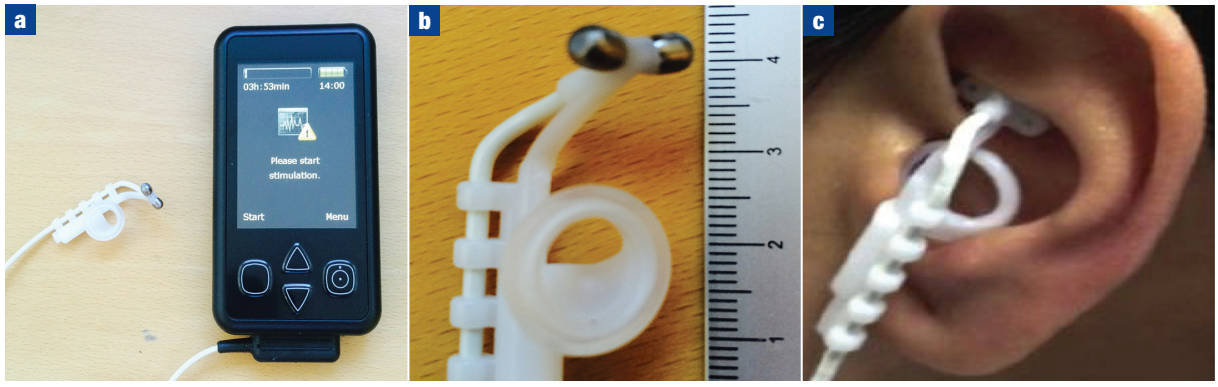
Figure 5. Non-invasive auricular vagus nerve stimulation. The device is placed in the inner aspect of the ear is connected to a stimulation generator, thereby providing stimulation to the auricular branch of the vagus nerve. **a.** Auricular electrode and stimulation device. **b.** Auricular electrode. **c.** Auricular electrode in situ.



Established clinical applications of vagus nerve stimulation

Epilepsy

Drug-refractory epilepsy is defined as that which has a poor clinical response to two or more antiepileptic drugs and occurs in up to one third of patients with epilepsy. In 1997, the United States Food and Drug Administration approved invasive left cervical vagus nerve stimulation as an adjunctive treatment in patients with refractory epilepsy. According to a UK-based meta-analysis, for every six implanted devices one patient derives benefit as defined by a 50% reduction in seizure frequency (Forbes et al, 2003). Based on this number needed to treat of six, vagus nerve stimulation appears to be an acceptable and cost-effective form of adjuvant treatment, largely through a reduction in emergency admissions (Forbes et al, 2003). A recent study in 76 patients with drug-refractory epilepsy using non-invasive auricular vagus nerve stimulation demonstrated a mean reduction of 23.4% in seizure frequency compared to an active control of low frequency stimulation after 28 days of treatment (Bauer et al, 2016).

The exact antiepileptic mechanism of action of vagus nerve stimulation is incompletely understood but it has been proposed that it results in desynchronization of aberrant cortical neuronal activity as well as modulating neurotransmitter release. The vagus nerve's particular anatomy provides a readily accessible conduit in which to influence the brain without recourse for intracranial neurosurgery. However, full efficacy can be delayed such that its maximal effect may not be observed until 2 years after implantation (Morris and Mueller, 1999). Nevertheless, further studies are warranted to evaluate the efficacy of right-sided, and even bilateral, vagus nerve stimulation to objectively ascertain if outcomes can be improved.

Headache and migraine

Headaches are the most prevalent neurological disorder, with approximately half of the population having a headache during a given 12-month period. The population prevalence of migraine has been estimated to be in the order of 18% (Jensen and Stovner, 2008), although it is likely that tension-type headache is more common. Migraine is characterized by an intense, unilateral and pulsatile headache that is frequently preceded by an aura that is most commonly visual, but can be sensorimotor or verbal in nature. Cortical spreading depression, a self-propagating wave of depolarization that spreads across the cerebral cortex, is considered to be one of the key electrophysiological events underlying migraine aura and is a frequently a trigger for headache per se.

In animal models, both invasive and non-invasive vagus nerve stimulation reduce the rate of cortical spreading depression and induce a two-fold increase in the stimulus needed to provoke this phenomenon (Chen et al, 2016). In a randomized controlled trial in patients with chronic migraine, Straube et al (2015) demonstrated that low frequency (1 Hz) auricular non-invasive vagus nerve stimulation was superior to high frequency (25 Hz) in reducing the number of headache days over the final 28 days of the study in comparison to the baseline phase. However, it must be noted that in this study low frequency vagus nerve stimulation was designed to be the active control intervention.

In a further study in chronic cluster headache, Gaul et al (2016) compared adjunctive prophylactic cervical non-invasive vagus nerve stimulation to standard of care, and showed that vagus nerve stimulation had a mean therapeutic gain of 3.9 fewer headache attacks per week. In a small 3-month, open-label, prospective observational study using cervical non-invasive vagus nerve stimulation, Kinfe et al (2015) demonstrated meaningful reductions in duration, frequency and intensity of treatment-refractory migraine but also improvement in sleep quality and a reduction in depression scores. In all of these studies, there were no serious treatment-related adverse events with either method of non-invasive vagus nerve stimulation. A recent study has provided evidence that in chronic cluster headache, vagus nerve stimulation is associated with enhanced health benefits for lower overall cost than standard of care (Morris et al, 2016). Although

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headache represents a promising indication for vagus nerve stimulation, further larger well-designed randomized controlled trials are needed to establish the indications most likely to benefit from treatments with vagus nerve stimulation, the optimal dosing regimen and finally type of stimulation, e.g. prophylactic or as required.

Potential clinical applications of vagus nerve stimulation

Heart failure

Heart failure is a leading cause of health-care utilization and despite advances in clinical evaluation long-term survival rates remain poor. There has also been a paucity of new drug treatments. It has been recognized for some time that in patients with chronic heart failure there is autonomic imbalance such that there is relatively high sympathetic tone coupled with paucity of vagal activity. Thus therapies aimed at restoring this imbalance, such as vagus nerve stimulation, are intuitively an attractive therapeutic target. It has been proposed that chronic vagus nerve stimulation indirectly modulates intrinsic neurons within the myocardium given their propensity for neuronal plasticity (Kember et al, 2014).

In a recent multicentre study in patients with moderate to severe heart failure, defined by New York Heart Association class III and ejection fraction of <40%, 707 patients were randomized to standard of care or invasive vagus nerve stimulation (CardioFit). The co-primary end points were time to death or time to first event of worsening heart failure (Gold et al, 2016). The primary outcome occurred in 30.3% of the active group against 25.8% of the standard of care group (hazard ratio 1.14, 95% confidence interval 0.86–1.53, P=0.37). This rigorously performed study provides robust evidence that invasive vagus nerve stimulation is not efficacious in the treatment of moderate to severe heart failure.

Immune-mediated inflammatory disorders

Immune-mediated inflammatory disorders, such as inflammatory bowel disease, rheumatoid arthritis and asthma, are common and are associated with significant health-care costs and a reduction in quality of life. Treatments directed towards modifying the inflammatory response, such as anti-TNF-α agents, are efficacious but are expensive, can require hospital admission for their administration and can be associated with severe side effects. As discussed, TNF represents a central pro-inflammatory facet of the cholinergic anti-inflammatory pathway. Therefore it has been proposed that vagus nerve stimulation may offer a novel non-pharmacological neuro-immuno-modulatory anti-inflammatory treatment via stimulation of the cholinergic anti-inflammatory pathway.

Inflammatory bowel disease

In a recent preliminary study in patients with Crohn's disease, Bonaz et al (2016) demonstrated that 6 months of invasive vagus nerve stimulation resulted in five out of seven patients improving their vagal tone, as measured by heart rate variability, as well as 'evolving' towards remission across clinical, biological, and endoscopic aspects. While these preliminary results provide a signal as to the potentially efficacy of this immune-neuro-modulatory approach, further work is warranted to examine these findings in a larger well-designed study.

Rheumatoid arthritis

Koopman et al (2016) recently reported data from 17 patients with rheumatoid arthritis who had invasive vagus nerve stimulation. After 6 weeks there was a significant reduction in levels of pro-inflammatory cytokines and validated disease activity scores. Notably, however, when the stimulation was discontinued after 6 weeks there was a rebound increase in disease activity. These results need to be replicated in further placebo studies.

Pain

There is increasing appreciation of the role of the vagus in mediating anti-nociception, particularly within the viscera. Studies in vagotomised rats have suggested that electrical vagus nerve stimulation, applied distal to the severance, reduces visceral pain to standardized mechanical visceral distension (Chen et al, 2008). Deep slow-paced breathing is known to increase vagal tone via the Hering Breuer reflex. The authors have previously demonstrated in healthy subjects that deep breathing during distal oesophageal acidification prevents the development of oesophageal pain hypersensitivity, as a result of central sensitization (Botha et al, 2015). Busch et al (2013) found that non-invasive auricular vagus nerve stimulation increased mechanical and pressure pain thresholds and reduced mechanical pain sensitivity in healthy volunteers.

In an important and innovative study, Napadow et al (2012) sought to combine both physiological elevation of vagal tone, which occurs during the inspiratory phase of the respiratory cycle, with non-invasive auricular vagus nerve stimulation in what the authors term 'respiratory gated auricular vagal afferent nerve stimulation' (RAVENS), such that inspiration triggers non-invasive electrical auricular vagal stimulation. A total of 18 patients with chronic pelvic pain as a result of endometriosis were randomized to non-invasive auricular vagus nerve stimulation or RAVENS and underwent somatic quantitative sensory testing in a crossover design. While both vagus nerve stimulation and RAVENS reduced pain sensitivity, this reduction was superior following RAVENS. In addition, Frøkjaer et al (2016) have recently demonstrated that combined deep slow breathing and non-invasive auricular vagus nerve stimulation, albeit not respiratory gated, reduces somatic pain sensitivity and enhances gastroduodenal motility. Further work is needed in developing this novel and mechanistically based concept of combined physiological and electrical elevation of vagal tone.

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KEY POINTS

- The vagus nerve exerts important functions including regulating homeostasis, modulating gastrointestinal secretion and motility as well as inflammatory and anti-nociceptive effects.
- Vagus nerve stimulation has been proposed as a therapeutic intervention across a number of prevalent clinical disorders including epilepsy and migraine.
- A number of techniques are available for vagus nerve stimulation including invasive and non-invasive or transcutaneous techniques.

Table 1. Issues that need to be addressed with regard to the design and conduct of future vagus nerve stimulation studies

Appropriate study design to address device efficacy potentially using 'hard' clinical end points
Development of robust placebo devices or interventions
Determination of optimal stimulation parameters
Determination of optimal dosing frequency
For non-invasive vagus nerve stimulation determining whether stimulation should be unilateral or bilateral and whether it is safe to stimulate bilaterally
Whether the concomitant administration of physiological modulation of vagal tone, with deep slow paced breathing for instance, has an additive therapeutic effect
Rates of longer term adverse effects of vagus nerve stimulation
Early phase 2 pilot studies need to focus on mechanism of action rather than efficacy outcomes per se
Translating the results of positive pilot studies into robustly designed phase 3 studies
Avoiding the initial study of patients with the most severe or treatment-refractory disease

Pitfalls and problems of vagus nerve stimulation

Given its widespread distribution throughout a large proportion of the body, it should not be surprising that the vagus nerve has been implicated in the pathophysiology of a number of disorders. Indeed, there is a strong argument that vagal dysfunction is a pivotal pathophysiological feature in both explained, i.e. organic, and unexplained functional disorders, and the authors advocate the encompassing term 'vagalopathy' in this regard. The inherent attractiveness of vagus nerve stimulation as a therapeutic modality has generated considerable enthusiasm, particularly in disorders where patients are refractory to standard interventions. However, this enthusiasm must be tempered as in many areas the evidence base is very limited and further well-designed placebo-controlled trials are needed. Furthermore, large numbers of trial participants will generally be needed to demonstrate efficacy given the relatively high placebo response, particularly in the medically unexplained functional disorders. Innovative trial designs including randomized withdrawal phases will help to tease out many of these issues. *Table 1* lists the issues which, in the authors' opinion, need to be adequately addressed in order to move this technology from being a scientific curiosity to a routine clinical treatment. Clearly, the answers to these various issues will vary from disorder to disorder but future studies must be conducted with appropriate scientific rigour for results to be clinically meaningful and therefore, by extension, applicable.

Conclusions

The vagus nerve continues to be an area of pathophysiological interest across a number of clinical disciplines. By extension, vagus nerve stimulation had generated great interest and continues to be actively investigated. However, despite initial promising results across many of these areas, there are a number of pitfalls and outstanding knowledge gaps that need to be addressed, as it is unlikely that vagus nerve stimulation represents a therapeutic panacea. Nevertheless, vagus nerve stimulation is a potential treatment option that needs to be investigated although its absolute place in clinical practice remains to be fully determined. **BJHM**

Conflict of interest: Dr AD Farmer received a speaker fee from Electrocore LLC in June 2015. Electrocore LLC manufacture the Gammacore vagus nerve stimulation device. Dr AD Farmer is supported by the Pain Relief Foundation and the Danish Diabetes Academy founded by the NovoNordisk Foundation. Dr A Albu-Soda is a doctoral fellow funded by the People Programme of the European Union's Seventh Framework Programme under REA grant agreement no. 607652 (NeuroGut). None of the funders had any input into the preparation, revision or submission of this manuscript.
Statement of contributions: Dr AD Farmer: drafting of the manuscript, critical revision of the manuscript for important intellectual content; Dr A Albu-Soda: drafting of the manuscript; critical revision of the manuscript for important intellectual content; Professor Q Aziz: critical revision of the manuscript for important intellectual content.

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