REVIEW ARTICLE

Surgically implanted and non-invasive vagus nerve stimulation: a review of efficacy, safety and tolerability

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Vagus nerve stimulation (VNS) is effective in refractory epilepsy and depression and is being investigated in heart failure, headache, gastric motility disorders and asthma. The first VNS device required surgical implantation of electrodes and a stimulator. Adverse events (AEs) are generally associated with implantation or continuous *on–off* stimulation. Infection is the most serious implantation-associated AE. Bradycardia and asystole have also been described during implantation, as has vocal cord paresis, which can last up to 6 months and depends on surgical skill and experience. The most frequent stimulation-associated AEs include voice alteration, paresthesia, cough, headache, dyspnea, pharyngitis and pain, which may require a decrease in stimulation strength or intermittent or permanent device deactivation. Newer non-invasive VNS delivery systems do not require surgery and permit patient-administered stimulation on demand. These non-invasive VNS systems improve the safety and tolerability of VNS, making it more accessible and facilitating further investigations across a wider range of uses.

Introduction

Vagus nerve stimulation (VNS) is a viable treatment option in refractory epilepsy and depression [1]. Until recently, all VNS therapy required surgical implantation of electrodes (around the cervical vagus nerve) connected to a stimulating device implanted under the anterior chest wall [1,2]. Implantable VNS is safe and well tolerated [1], but adverse events (AEs) are associated with both the surgical procedure and the electrical stimulation itself [1,3]. Subsequently, non-invasive VNS (nVNS) delivery options that eliminate the need for surgical implantation were developed. These alternative VNS delivery systems avoid surgery-related AEs (e.g. infection, cardiac events) and may limit AEs related to the continuous *on–off* stimulation cycle of implantable devices, since nVNS devices can be adjusted to balance efficacy and tolerability [4,5].

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This review provides a summary of the efficacy, safety and tolerability of VNS delivery systems including both surgically implantable VNS and newer devices in development that deliver VNS non-invasively.

Vagus nerve function and anatomic connections

The vagus (tenth cranial) nerve is a mixed parasympathetic nerve, containing both afferent and efferent sensory fibers. An estimated 80% of vagus nerve fibers are afferent and convey visceral, somatic and taste sensations (Fig. 1) [6–9]. The vagus nerve is subdivided into five groups: (1) special visceral afferents, (2) general visceral afferents, (3) general somatic afferents, (4) special visceral efferents and (5) general visceral efferents [10]. Thorough reviews of vagus nerve anatomy and function have been discussed previously [11,12]. The vagus nerve connections allow it to modulate the function of higher brain centers, forming the basis for its potential use in many disorders.

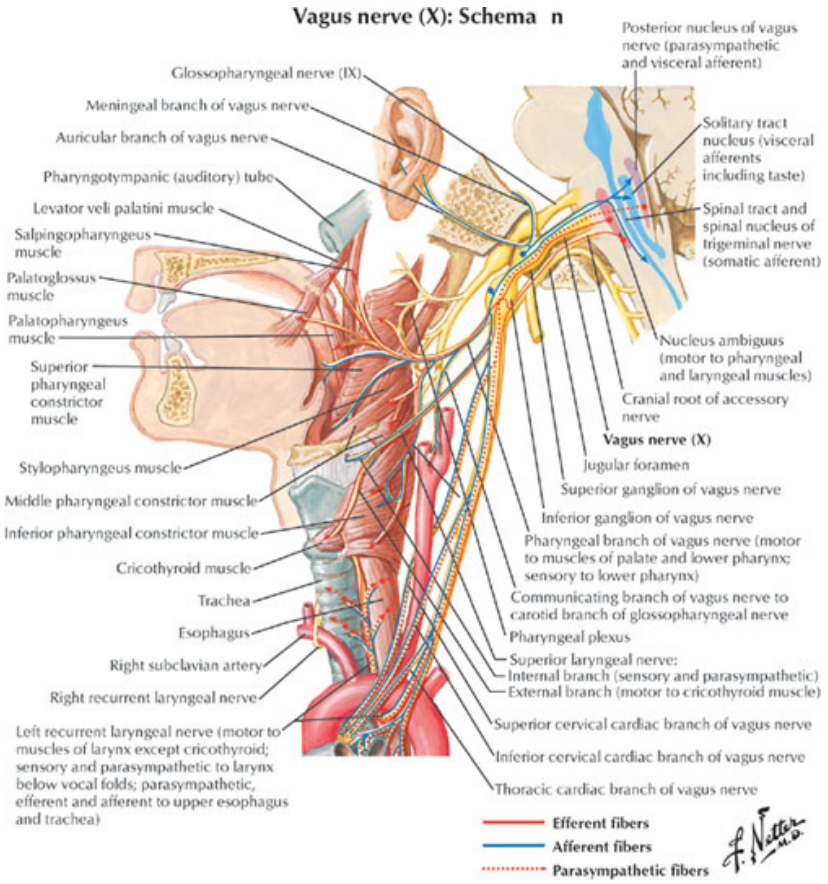

Figure 1 Vagus nerve innervation. (Reprinted with permission from Massey [9]).

Effectiveness of implantable VNS

VNS Therapy system

Early animal studies supported VNS effectiveness in human epilepsy [13–16]. Clinical studies of the implantable VNS Therapy system (Fig. 2a; Cyberonics, Inc., Houston, TX, USA) in refractory epilepsy demonstrated 50% seizure reduction in 24.5%–46.6% of patients [2,17,18]. The VNS Therapy system was approved for the treatment of medically refractory epilepsy in Europe in 1994 and in the USA and Canada in 1997. As of August 2014, over 100 000 VNS devices were implanted in more than 75 000 patients worldwide [19].

Mood improvements observed in patients who received implantable VNS for refractory epilepsy [20,21] led to investigations of treatment-resistant depression. A large sham-controlled, 10-week trial in treatment-resistant depression failed to find a statistical difference between the two treatments in terms of the 24-item Hamilton Depression Rating Scale ($HRSD_{24}$) response [22]. However, a 1-year open-label extension ($n = 205$) found that the $HRSD_{24}$ score improved significantly by 0.45 (standard error = 0.05) points per month (repeated measures $t = 8.25$, degrees of freedom 654, $P < 0.001$) [23]. This led to US Food and Drug Administration (FDA) approval of implantable VNS for the adjunctive, long-term treatment of chronic or recurrent depression in patients at least 18 years of age who are experiencing an episode of major depression and have not had an adequate response to four or more antidepressant treatments [24].

Implantable VNS provided efficacy benefits in small studies in refractory migraine and cluster headache (CH) [25,26], heart failure [27], Alzheimer's disease [28,29], treatment-resistant anxiety disorders [30] and obesity [31]. The exact mechanism by which VNS provides benefit across these widely different conditions is unknown. The diverse therapeutic potential of VNS, along with the AEs, cost and limited accessibility associated with implantable VNS, led to the development of new nVNS modulators that do not require surgery.

Safety and tolerability associated with the surgically implanted VNS Therapy system can be divided into two classes: device implantation related and VNS stimulation related [1,3].

The most frequent surgical AEs include infection (3%–6% of patients), vocal cord paresis, lower facial

weakness and, infrequently, bradycardia and asystole [32]. Infection rarely prompts device removal [33]. Vocal cord paresis and lower facial weakness have occurred in about 1% of patients each [32,33]. With surgical technique improvements, permanent voice alterations and lower facial weakness have become rare. Depending on the duration of use, replacement of the stimulus generator battery will be required, necessitating additional surgery.

Stimulation-related AEs in refractory epilepsy and depression were similar and most frequently included voice alteration, cough, dyspnea, paresthesia, headache and pain (Table 1) [3]. The frequency of these AEs declines with continued treatment [34]. For example, voice alteration was present in 62% of patients with epilepsy receiving VNS at 3 months but in only 18.7% of patients at 5 years [3].

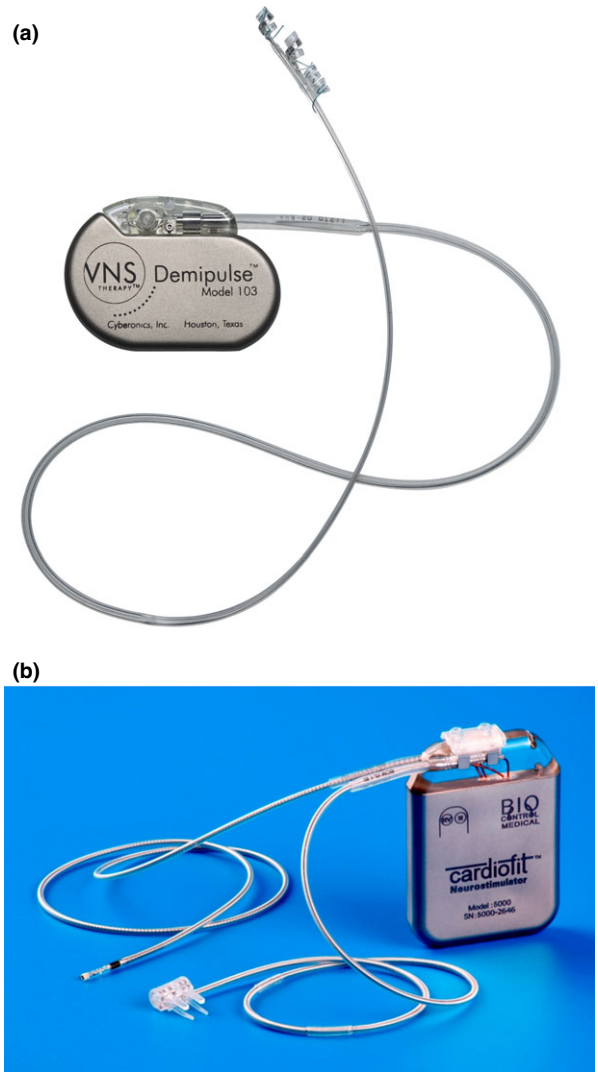

Figure 2 Implantable VNS systems: (a) VNS Therapy system and (b) CardioFit. (Reprinted with permission from (a) Cyberonics, Houston, TX, USA, and (b) BioControl Medical, Yehud, Israel).

Cardiac AEs associated with implantable VNS devices mainly occur in the operating room during initial device testing. These include bradycardia, ventricular asystole and complete heart block [35–38]. Only rarely have these emerged years after VNS initiation. One patient developed bradyarrhythmia characterized by sudden falls, pallor and unconsciousness lasting <10 s that occurred for the first time 2 years after VNS initiation. The attacks occurred during stimulation and stopped when the VNS device was turned off [39]. Another report described intermittent self-terminating complete heart block occurring every 15–25 min and lasting 20–40 s that occurred 6.5 years after the implantation of a VNS device for the treatment of epilepsy [40]. A third case reported periodic asystole 9 years after implantation [41].

VNS is not associated with central nervous system AEs such as fatigue, psychomotor retardation, cognitive dysfunction or suicidal ideation in patients with epilepsy. One suicide and seven suicide attempts in six patients occurred in the pivotal implantable VNS trial [23] in treatment-resistant depression. No teratogenicity has been observed [42,43]. Patients treated with implantable VNS have noted improvements in feelings of well-being, alertness, memory and thinking skills, as well as mood.

CardioFit

CardioFit (BioControl Medical Ltd., Yehud, Israel) (Fig. 2b) is an implantable VNS device being investigated in heart failure acting by preferential activation of vagal efferent fibers [44]. The rationale of this approach has been reviewed elsewhere [45,46]. The stimulation is designed to correct the autonomic imbalance (sustained sympathetic overdrive and parasympathetic withdrawal) that is maladaptive in heart failure [27,45].

An initial feasibility study evaluated the safety of CardioFit in eight patients with New York Heart Association (NYHA) class II–III heart failure over 6 months [27]. CardioFit stimulation provided statistically significant improvements in NYHA II–III heart failure, especially at months 1 and 3 ($P < 0.01$), reduced left ventricular end systolic volume ($P = 0.03$) and improved 6-min walking test ($P = 0.04$) and Minnesota quality of life measure ($P = 0.001$). Mild, transient voice alteration was the only implantation-associated event [27]. Stimulation-associated AEs included cough ($n = 4$), pain at stimulation site ($n = 4$), mandibular pain ($n = 3$) and voice alteration ($n = 2$). No AEs were severe; all resolved with continued treatment [27].

Table 1 Adverse events (%) reported in clinical trials of the VNS Therapy system in patients with epilepsy or depression (reprinted with permission from Ben Menachem [3])

Adverse event	3 months		12 months	5-year follow-up
	Epilepsy	Depression	Epilepsy	Epilepsy
Cough	21		15	1.5
Voice alteration	62	60	55	18.7
Dyspnea	16	23	13	2.3
Pain	17	27	15	4.7
Paresthesia	25		15	1.5
Headache	20	30	16	–
Pharyngitis	9		10	–
Depression	3		5	–
Infection	4	3	6	–
Deaths			2 patients (1 SUDEP, 1 pneumonia)	4 patients (1 SUDEP, 3 status epilepticus)

SUDEP, sudden, unexpected, unexplained death in epilepsy.

Subsequently, a phase 2 open-label, 6-month study ($n = 32$) in patients with NYHA II–IV heart failure had similar findings. Statistically significant effects were found between baseline and 6-month follow-up for NYHA class improvement ($P < 0.001$), 6-min walking ($P = 0.0014$), quality of life ($P = 0.0001$), left ventricular ejection fraction ($P = 0.0003$) and left ventricular end systolic volume index ($P = 0.02$).

In total, 26 serious AEs (SAEs) occurred in 13 patients. Two SAEs (acute pulmonary edema; surgical revision necessitated by a loose electrode connector on the stimulus generator) were implantation related [47]. A third SAE, an episode of syncope associated with new onset atrial fibrillation and hypotension, was felt to be possibly related to the system. Other SAEs possibly related to the procedure or the system included syncope facilitated by dehydration (two episodes) or new onset atrial fibrillation and hypotension (one episode), and atrial fibrillation (two episodes in the same patient; one episode recurred after cardioversion) [47].

Effectiveness of non-invasive VNS devices

NEMOS

NEMOS (Cerbomed, Erlangen, Germany) is an external device that provides transcutaneous VNS (tVNS) by using a dedicated intra-auricular electrode (like an earphone) which stimulates the auricular branch of the vagus nerve (Fig. 3a) [48]. In 2010, the device received the European clearance (CE mark) for epilepsy and is available in Germany, Austria, Switzerland and Italy. The patient controls VNS stimulation intensity within a defined range and self-treatment sessions lasting 1–4 h three to four times daily and as necessary (e.g. before a seizure) are recommended. Users adjust the current until they feel a slight discomfort or tingling sensation at the stimulation site [48].

A proof-of-concept study of NEMOS tVNS enrolled 10 patients with pharmacoresistant epilepsy who received treatment three times daily (1 h each) for 9 months [49]. Three patients discontinued [49]. Five of the seven patients who continued reported reductions in seizure frequency, but none reached the 50% reduction threshold for response. Two patients reported increased seizure frequency that remained constant over the entire study duration [49].

In another study in healthy volunteers ($n = 48$), tVNS increased mechanical and pressure pain threshold, reduced mechanical pain sensitivity and lowered pain ratings during sustained application of painful heat compared with sham treatment [50]. There were no clinically relevant AEs.

Napadow *et al.* [51] compared the effect of NEMOS stimulation to non-vagal auricular stimulation in patients ($n = 18$) with chronic pelvic pain. Although a numerical reduction in evoked pain intensity and temporal summation of mechanical pain was observed with NEMOS, the differences were not significant between the two methods. Anxiety was significantly reduced with NEMOS stimulation vs. non-vagal auricular stimulation. No significant effect of stimulation, time or interaction on heart rate or heart rate variability ($P > 0.7$) or on respiratory rate ($P > 0.8$) was observed.

gammaCore

gammaCore (electroCore LLC, Basking Ridge, NJ, USA) is a handheld, self-contained nVNS device under investigation for headache, epilepsy and gastrointestinal disorders. It consists of a portable stimulator with a battery, signal-generating and -amplifying electronics and a digital control user interface that controls signal amplitude (Fig. 3b). Two stainless steel round discs function as skin contact surfaces that deliver a proprietary, low-voltage electrical signal to the cervical vagus nerve. The device delivers a programmable number of stimulation cycles, each lasting 120 s [52].

Evidence for gammaCore nVNS efficacy comes from small studies in intractable CH [53], episodic migraine [54] and chronic migraine [55]. In CH, gammaCore nVNS delivered both acutely for CH attacks and as a twice-daily preventive treatment (median 12 weeks) was tested over a median of 12 weeks in 31 evaluable adults (12 with chronic CH, 10 as medically intractable CH, and nine with episodic CH). Overall, 18 of 21 patients reported improvement (51% mean improvement from baseline) and three reported no

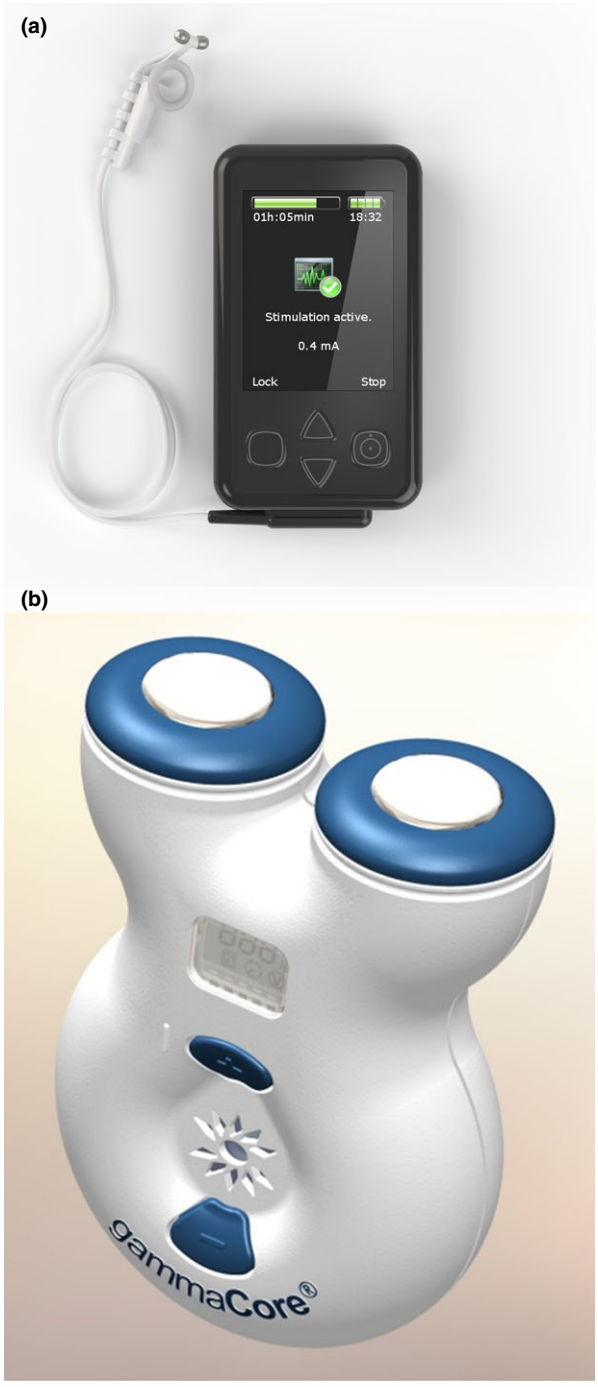

Figure 3 Non-implantable VNS systems: (a) NEMOS (tVNS) and (b) gammaCore (nVNS). (Reprinted with permission from (a) Cerbomed, Erlangen, Germany, and (b) electroCore, Basking Ridge, NJ, USA).

change. Seventeen were able to stop, reduce or significantly reduce their prior abortive treatment use [53]. AEs included local discomfort, a mild skin irritation secondary to the conductive gel and worsening of pain in one subject [52].

An open-label pilot study [4] of gammaCore nVNS in episodic migraine ($n = 30$) investigated applying two 90-s stimulations administered 15 min apart during migraine. Overall, 27 patients treated 80 migraines. Of 19 patients with moderate or severe pain at the time of treatment of their first attack, nine (47%) reported pain relief and four (21%) reported being pain free 2 h after treatment. In 54 migraine attacks that were moderate to severe at the time of treatment, 2-h pain relief was achieved in 23 (43%) attacks and 2-h pain-free status was achieved in 12 (22%). Treatment-related AEs, all mild or moderate, included transient muscle stiffness/pain ($n = 7$) and dizziness ($n = 2$); all AEs except one (neck stiffness treated with a nonsteroidal anti-inflammatory drug) resolved without treatment [4].

Moscato and Moscato [55] evaluated 73 patients with chronic migraine, 19 of whom had moderate to severe migraine pain with nausea, phonophobia and photophobia at the time of evaluation and received gammaCore nVNS in two 90-s treatments administered 15 min apart. At 2 h, mean visual analog scale pain scores were significantly reduced from baseline ($P < 0.05$); nine of 19 patients were pain free, six had reduced pain and four remained unchanged. AEs included two reports of brief paresthesia, which resolved within a few minutes [55]. gammaCore is now being evaluated in four multicenter, randomized, controlled trials in the EU and North America in primary headache disorders; to date, no significant serious device-related AEs have been reported. Table 2 summarizes the clinical studies of new implantable and non-implantable VNS devices covered in this review [4,27,47,49,50,52,53,55–58].

Discussion – safety and tolerability

VNS is well tolerated in the treatment of refractory epilepsy and depression [1]. Most AEs resolve after 1–2 years of continued treatment [3]. Implantable VNS is associated with surgically related AEs, such as infection and dysrhythmias; stimulation-associated AEs include cough, paresthesia, pain and voice alteration, which generally decrease in prevalence over time. Voice alteration, a common and particularly disturbing AE that may continue in nearly 20% of patients at 5 years, may be a consequence of the continuous *on–off* stimulation cycle seen with implantable VNS and is stimulus dose dependent. nVNS devices could be expected to provide an improved safety profile because they do not require surgical implantation and provide shorter durations of stimulation compared with the constantly cycling stimulation with implantable VNS.

Table 2 Summary of clinical studies utilizing implantable or non-invasive VNS delivery cited in this review

Reference	Indication studied	*n*	Stimulation schedule; location	Efficacy	Safety/tolerability
Schwartz *et al.* [27]	Severe congestive heart failure	8	2–10 s *on*, 6–30 s *off* for 6 months; right cervical vagus nerve	Significant improvements in NYHA class ($P < 0.01$), QOL on Minnesota Living With Heart Failure questionnaire ($P = 0.001$), and left ventricular end systolic volume ($P = 0.03$)	Implantation-related AE: voice alteration (hoarseness) Stimulation-related AEs: cough; pain at stimulation site, mandible and ear; voice alteration
De Ferrari *et al.* [47]	Chronic heart failure	32 (8 from feasibility phase [27] and 24 from multicenter international phase [47])	Duty cycle[a] ≤25% (e.g. maximum 10 s *on*, 30 s *off*) for 6 months; right cervical vagus nerve	At 3 and 6 months: 56% and 59% of patients improved by ≥1 NYHA class ($P \leq 0.001$) At 6 months: significant improvements in 6-min walk test ($P = 0.0014$), QOL on Minnesota Living with Heart Failure questionnaire ($P = 0.0001$), LVEF ($P \leq 0.0003$) and LVESVI ($P = 0.02$)	Implantation-related SAEs: acute pulmonary edema (1 event), surgical revision (1 event) Other possibly related SAEs: dehydration-related syncope (2 events); syncope resulting from new-onset atrial fibrillation and hypotension; atrial fibrillation (2 events; 1 was a return to atrial fibrillation after cardioversion) AEs: pain at site of stimulation ($n = 6$), cough ($n = 5$), dysphonia ($n = 4$), mandibular pain ($n = 3$) and ECG stimulus artifact ($n = 1$)
Ben-Menachem *et al.* [57]	Refractory focal epilepsy	5	12–15 months after implantation: amplitude was 1.5–2.0 mA, frequency was 20 Hz, duty cycle[a] was 30 s *on*, 1.8–3 min *off* (14.3%–20.3%) with a pulse width of 0.3 ms and a quasi-trapezoidal pulse shape; left cervical vagus nerve	Seizure frequency reduction of 50% in 2 patients and 25% in 2 patients; rate unchanged in 1 patient	Cough and/or hoarseness not noted until stimulation of 2 mA reached
Stefan *et al.* [49]	Pharmacoresistant epilepsy	10	3 times daily (1 h each) for 9 months; left auricular branch of vagus nerve	50% reduction threshold not reached; seizure frequency was reduced by 45% and 48% in 2 patients and increased in 2 patients	3 patients discontinued; AEs included hoarseness, headache and constipation
Busch *et al.* [50]	Healthy volunteers	48	Stable stimulation duration of ~1 h; left auricular branch of vagus nerve	tVNS increased pain threshold and lowered pain sensitivity and pain ratings	No discontinuations or SAEs; AEs included stimulation site sensations of slight pain, pressure, prickling, itching or tickling in 39 patients with active stimulation
Hein *et al.* [58]	Major depression	37	15 min once or twice daily, 5 day/week for 2 weeks; bilateral transauricular vagus nerve	Significant reduction ($P < 0.0001$) in Beck Depression Inventory (self-report) but not in clinician-rated Hamilton Depression Rating Scale between active and sham treatments	No vital sign changes; no unpleasant sensations or irritations

(continued)

Table 2 *(Continued)*

Reference	Indication studied	*n*	Stimulation schedule; location	Efficacy	Safety/tolerability
Nesbitt *et al.* [52,53]	Intractable CH	21	Acute stimulation of 2–4 cycles (90 s each) to abort CH attacks and twice daily as preventive; cervical vagus nerve, ipsilateral to pain	Overall improvement: estimated subjective improvement of 51% in 18 patients; no change in 3 patients Abortive treatment: 47% of acute attacks were terminated and 27% substantially improved in 15 min Preventive treatment: reduction in 24-h attack frequency (4.68 ± 2.36 to 2.54 ± 2.12; $P < 0.0005$)	AEs included worsening of pain in 1 patient; skin irritation, local skin reaction to conductive gel
Goadsby *et al.* [4]	Episodic migraine	30	Two 90-s stimulations 15 min apart; right cervical vagus nerve	Pain relief noted at 2 h for 46 of 79 migraines (58%) treated by 26 patients; 2-h pain free rate was 28%	AEs included transient muscle or local skin irritation and 2 reports of light-headedness
Moscato and Moscato [55]	Chronic migraine	19	Two 90-s stimulations 15 min apart; location not reported	Reduction ($P < 0.05$) in mean pain scores in overall group at 2 h; 9 patients were pain free, 6 had reduced pain and 4 were unchanged at 2 h	2 brief episodes of paresthesia

AE, adverse event; CH, cluster headache; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end systolic volume index; NYHA, New York Heart Association; QOL, quality of life; SAE, serious adverse event; tVNS, transcutaneous VNS; VNS, vagus nerve stimulation.
[a]Duty cycle is the percentage of time that stimulation is *on*.

Efficacy could not be compared between these modalities at the time of this review because of the different stages of development of the various delivery systems. One consistent observation, however, is that efficacy and possible AEs, at least for epilepsy and depression, improve with time over a period of about 18 months [23,32,34,59–61].

Implanted VNS devices are currently approved for the treatment of refractory epilepsy and depression; past and ongoing investigations in other indications have provided signals of the therapeutic potential in a wide variety of conditions. AEs, amongst other factors stemming from the surgical procedure, are negative aspects of implantable VNS and could be eliminated entirely through the use of nVNS delivery devices. The less frequent stimulation schedules used with nVNS may reduce the overall incidence of stimulation-associated AEs. Without a requirement for an expensive and potentially risky surgical procedure, nVNS may facilitate the earlier use of therapeutic VNS without the prerequisite of achieving a 'treatment-refractory' status in the condition of interest. Results from ongoing clinical studies are awaited to help inform appropriate use.

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Disclosure of conflicts of interest

Dr Ben-Menachem reports serving on an advisory board for electroCore and as a consultant for Bial, BioControl, Esai, UCB Pharma; she also serves as an editor of *Acta Neurologica Scandinavica*. Dr Revesz has no conflict of interest related to the content of this article. Dr Silberstein reports serving on an advisory board for electroCore. Dr Simon reports being an employee of electroCore and has numerous issued patents and pending patent applications related to the gammaCore device.

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