Epilepsy & Behavior xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Vagus nerve stimulation (VNS) therapy update

James W. Wheless [a,b,*], Andrew J. Gienapp [c,d], Phillippe Ryvlin [e]

[a] Le Bonheur Comprehensive Epilepsy Program, Neuroscience Institute, Le Bonheur Children's Hospital, Memphis, TN, United States
[b] Department of Pediatrics, Pediatric Neurology Division, University of Tennessee Health Science Center, Memphis, TN, United States
[c] Medical Education, Methodist University Hospital, Memphis, TN, United States
[d] Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, TN, United States
[e] Department of Clinical Neurosciences, Lausanne University Hospital, Lausanne, Switzerland

ARTICLE INFO

Article history:
Accepted 15 June 2018
Available online xxxx

Keywords:
VNS therapy
Epilepsy
Intractable
Vagus nerve stimulation
Neurostimulation

ABSTRACT

Epilepsy affects millions of people worldwide. Approximately one-third have pharmacoresistant epilepsy, and of these, the majority are not candidates for epilepsy surgery. Vagus nerve stimulation (VNS) therapy has been an option to treat pharmacoresistant seizures for 30 years. In this update, we will review the clinical data that support the device's efficacy in children, adolescents, and adults. We will also review its side-effect profile, quality of life and cost benefits, and the impact the device has on sudden unexpected death in epilepsy (SUDEP). We will then discuss candidate selection and provide guidance on dosing and future models. Vagus nerve stimulation therapy is an effective treatment for many seizure types and epilepsy syndromes with a predictable and benign side-effect profile that supports its role as the most commonly prescribed device to treat pharmacoresistant epilepsy.

This article is part of the Special Issue "Neurostimulation for Epilepsy".

1. Introduction

Epilepsy and seizures affect 1% of the population, accounting for nearly 3 million individuals in the United States, with approximately 200,000 new cases diagnosed each year. Although antiepileptic drugs (AEDs) are the primary form of treatment, outcome surveys continue to reveal only mixed success even with new AEDs that have unique mechanisms of action, some of which have become available over the past 25 years [1–3]. Approximately one-third of patients have seizures that are unresponsive to pharmacologic therapy [4–6]. In addition, safety and tolerability issues associated with both the acute and chronic side effects and toxicity complications further diminish the effectiveness of AEDs [7–13]. Nonadherence to AEDs, which is highly prevalent in populations with epilepsy, can also diminish treatment effectiveness and further increase mortality as well as significantly increase healthcare utilization [14]. Other treatment options (Fig. 1) are available for select subgroups of patients, including dietary therapy [15, 16] and epilepsy surgery, which may be an option to manage or lessen poorly-controlled seizures in 10% to 25% of patients with refractory epilepsy [17]. However, children and adults with uncontrolled seizures continue to carry a sad burden of higher mortality rates, higher rates of accidents and injuries, greater incidence of cognitive and psychiatric impairment, poor self-esteem, higher levels of anxiety and depression, and social stigmatization or isolation compared with the general population [18, 19]. The shortcomings of AEDs, dietary therapy, and epilepsy surgery in improving overall outcome highlight the need for other treatments (e.g., device therapy), one of which is vagus nerve stimulation (VNS) therapy.

Vagus nerve stimulation therapy is approved for the treatment of epilepsy without age or seizure type restrictions (in most countries) and for treatment-resistant depression in more than 70 countries around the world, including member nations of the European Union, Japan, Canada, Australia, the United States of America, and China. As of June 2018, more than 100,000 patients have received VNS therapy worldwide.

The VNS therapy system is comprised of a pulse generator, a bipolar VNS lead, a programming wand with accompanying software for a handheld computer, a tunneling tool, and handheld magnets [20, 21]. The generator transmits electrical signals to the vagus nerve through the lead (Fig. 2). The software allows placement of the programming wand over the generator for reading and altering stimulation parameters. While there are many possible parameter options available, guidance is provided to allow clinicians to start with the most common and efficacious settings for each generator model available (Tables 1a–1d). Each stimulation period is preceded by 2 s of ramp-up time, followed by 2 s of ramp-down time.

Five models of the VNS therapy generators are currently available. The Demipulse Model 103 (single pin) and the Demipulse Duo Model 104 (dual pin) (LivaNova USA, Inc., Houston, TX)—the dual-pin generator, Model 104, is for replacement procedures only in patients with the

* Corresponding author at: Le Bonheur Children's Hospital, 49 N Dunlap Ave, 3rd Floor FOB, Memphis, TN 38105, United States.
E-mail address: jwheless@uthsc.edu (J.W. Wheless).

https://doi.org/10.1016/j.yebeh.2018.06.032
1525-5050/

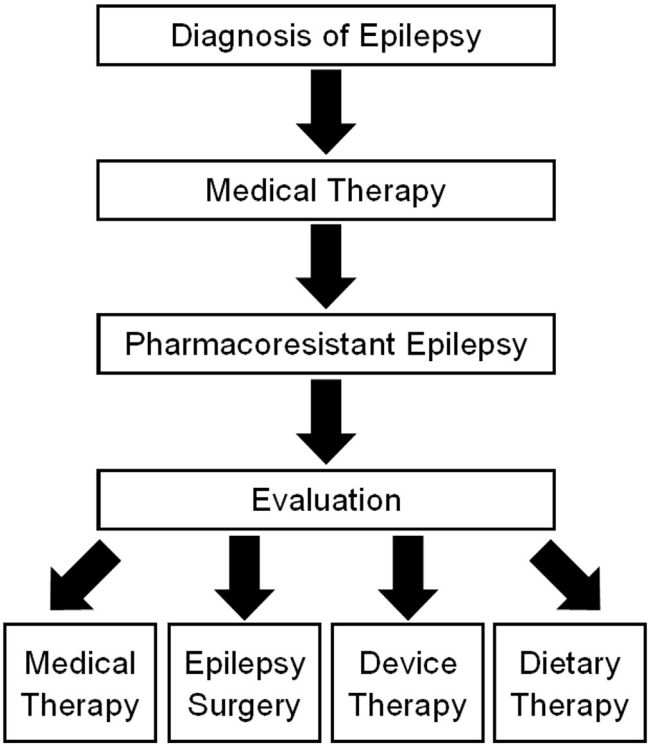

Fig. 1. Options for patients with refractory seizures. General approach to the treatment of the patient with epilepsy, and the four possible treatment options once they develop pharmacoresistant epilepsy (some patients may benefit from a combination of these).

previous dual-pin lead models. The newer AspireHC Model 105, AspireSR Model 106, and the SenTiva Model 1000 (LivaNova USA, Inc., Houston, TX), all of which are available in single pin only—different countries have differing models available (Figs. 3, 4). Currently, two leads are available: the Perennia Model 303 and PerenniaFLEX Model 304 (LivaNova USA, Inc., Houston, TX). The PerenniaFLEX is the lead used almost all of the time. All current lead models are single pin and come in two sizes (2.0 or 3.0 mm — the inner diameters of the helical coil) to account for various sizes of the vagus nerve.

Table 1a
VNS therapy stimulation variables and suggested therapeutic values (Models 103, 104, 105, 106, and 1000).

Parameter	Units	Range	Suggested settings
Output current	Milliamps	0–3.5	>1.50–2.25
Signal frequency	Hertz	1–30	20
Pulse width	Microseconds	130–1000	250
ON—time[a]	Seconds	7–60	30
OFF—time	Minutes	0.2–180	5
Magnet setting			
Output current	Milliamps	0–3.5	>1.75–2.25
Pulse width	Microseconds	130–1000	250
ON—time	Seconds	7–60	14

[a] Other duty cycle suggestions are 30 s on/3.0 min off, 30 s on/1.8 min off, or 7 s on/0.3 min off (for this setting, AutoStim must be turned off [Models 106 and 1000]).

The purpose of this review is to help the clinician decide which patients are the best candidates for VNS therapy and how to incorporate this treatment into a comprehensive epilepsy practice.

2. Efficacy

2.1. Adult efficacy: randomized controlled trials (regulatory and quality-of-life trials) and approval trials

Two pivotal randomized controlled trials demonstrated the efficacy of VNS versus sham stimulation in patients with drug-resistant focal epilepsy [22, 23] (Table 2). One of the studies (EO3) included 114 patients ≥12 years of age, all of whom were implanted with the same VNS device [22]. While the active treatment group received standard VNS (i.e., 30 Hz, 500 μs, 1.5 mA, 30 s ON, 5 min OFF), the control group underwent a supposedly sham stimulation (1 Hz, 130 μs, 1.25 mA, 30 s ON, 90 min OFF). The primary endpoint was the mean reduction in daily seizure frequency after 3 months of VNS therapy, which reached 24.5% in the active treatment group versus 6.1% in the control group ($p < 0.05$). The second study (EO5) used the same design and stimulation parameters as above in a series of 196 patients, 103 of whom received a sham stimulation and 95 received effective stimulation [23]. These two groups showed a mean decrease in daily seizure frequency at 3 months of follow-up of 15% and 28%, respectively ($p = 0.039$).

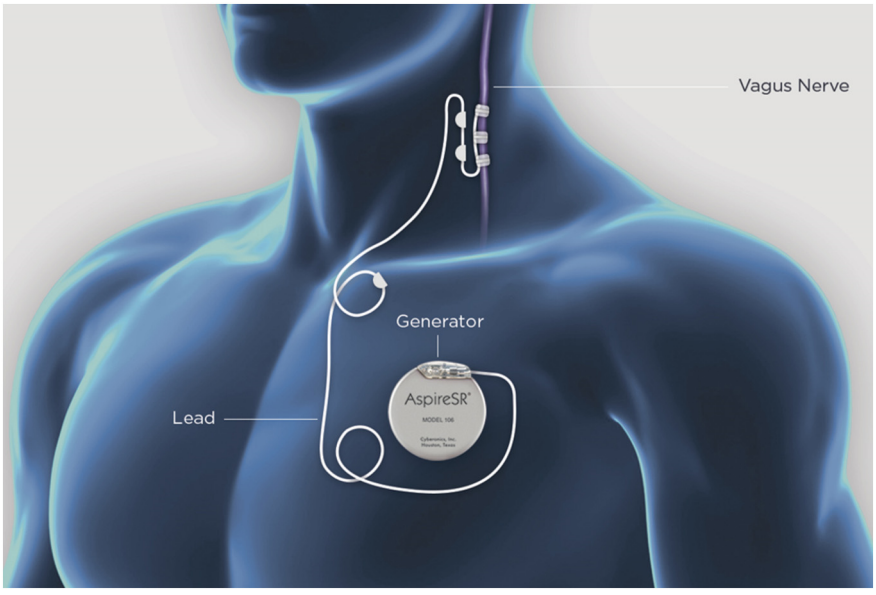

Fig. 2. VNS therapy: lead wire and generator.

Please cite this article as: Wheless JW, et al, Vagus nerve stimulation (VNS) therapy update, Epilepsy Behav (2018), https://doi.org/10.1016/j.yebeh.2018.06.032

Table 1b
Aspire SR (Model 106) and SenTiva (Model 1000) parameters and suggested therapeutic values.

Parameter	Units	Suggested settings
Output current	Milliamps	1.50–2.25
Signal frequency	Hertz	20
Pulse width	Microseconds	250
ON—time[a]	Seconds	30
OFF—time	Minutes	5.0
Magnet setting		
Output current	Milliamps	1.75–2.25
Pulse width	Microseconds	250
ON—time	Seconds	14

Magnet current is the same as or 0.25 mA above normal output current.
[a] Other duty cycle suggestions are 30 s ON/3.0 min OFF, 30 s ON/1.8 min OFF, or 7 s ON/0.3 min OFF (turn off AutoStim to use this setting.).

Following a large number of noncontrolled series, which suggested that VNS therapy improved quality of life (QoL), an open-label prospective randomized controlled study was performed to address this issue. Twenty-eight European and Canadian sites recruited 112 adults with refractory focal epilepsy, half of whom received VNS therapy in addition to best medical practice (BMP) while the other half were allocated to BMP alone. The primary endpoint was the mean change from baseline of the Quality of Life in Epilepsy Inventory-89 total score (QOLIE-89). Patients undergoing VNS associated with BMP showed a significantly greater improvement in QOLIE-89 than those receiving BMP alone ($p < 0.05$) [24].

Additionally, a 2-year follow-up of 5554 children and adults whose data were captured in the international VNS therapy patient outcome registry showed improvement as assessed by the treating physician for alertness, severity of postictal state, frequency of seizure cluster, mood, verbal communication, school/professional achievements, and memory. Quality of life improved significantly more in responders than in nonresponders [25].

In a large Japanese VNS registry (required for approval in Japan), including 362 children and adults, the 50% responder rate improved from 55.8% at 1-year follow-up to 57.7% at 2 years and 58.8% at 3 years [26]. In parallel, QoL improvement was seen in 44.3% at 1 year, 51.1% at 2 years, and 54.7% at 3 years. Another recent series of 85 adult patients treated with VNS therapy demonstrated a 54.1% responder rate at 18-month follow-up [27]. Conversely, a smaller prospective series of 39 adults followed-up for 1 year found that only 26% achieved a ≥50% reduction in seizure frequency [28].

2.2. Pediatric studies

Studies indicate that response to VNS therapy is independent of age, seizure type, or epilepsy syndrome. In a large consecutive series of 141 children 18 years of age and younger with treatment-resistant epilepsy and at least 1 year of follow-up, seizure frequency significantly improved with VNS therapy (mean reduction, 58.9%; $p < 0.0001$) [29]. The mean age at initiation of VNS therapy was 11.1 years (range, 1 to 18); 86 (61%) participants were under 12 years of age when they received VNS therapy. The mean duration of VNS therapy was 5.2 years (range, 25 days to 11.4 years). The overall responder rate for this population was 65%, with 41% experiencing 75% or greater reduction in seizure frequency. Comparisons between those older than 12 years of age and those younger than 12 years of age showed no differences in efficacy or safety between the groups. Additional pediatric studies showed similar findings with increasing response rates over time that were similar to those seen in the real-world outcome data for adults with VNS [30–35]. A retrospective study of 46 children implanted under the age of 18 (median age, 12.1 years) showed median seizure frequency reductions in the range of 60% over 3 years with VNS therapy with response rates more favorable among patients <12 years of age [31]. Particularly favorable results, including reduced seizure frequency and severity and improved QoL, have been reported among patients in open-label studies of Lennox–Gastaut syndrome and other refractory childhood epilepsies, such as hypothalamic hamartomas, epileptic encephalopathies, Rett syndrome, Dravet syndrome, and tuberous sclerosis complex [30, 36–57] (Tables 3, 4). Verbal performance, alertness, motor and cognitive functions, and general behavior improved, sometimes dramatically [37, 39, 46, 58, 59]. A retrospective study [59] showed that improved QoL (particularly in the area of alertness) was associated with VNS therapy in patients with autism ($n = 59$) or Landau–Kleffner syndrome (LKS) ($n = 6$), with more than half of the patients in each group also experiencing a 50% or more reduction in seizure frequency at follow-up (12-month follow-up for autism and 6-month follow-up for LKS). Studies have also shown both seizure frequency reductions and improved QoL among both institutionalized and noninstitutionalized patients with mental impairment/developmental delay [60, 61]. Vagus nerve stimulation therapy also successfully stopped a case of refractory generalized convulsive status epilepticus in a patient 13 years of age [62]. Another report of 3 children admitted to the intensive care unit (ICU) after developing status epilepticus showed that VNS therapy allowed early cessation of status and discharge from the ICU [47].

Open studies indicate that VNS is a favorable treatment option for a wide range of patients regardless of age or seizure type [29, 63–71]. A meta-analysis of VNS therapy efficacy showed that children and those patients with generalized epilepsy benefited significantly from VNS therapy [69]. A study of stimulation parameters among patients of different ages [72] recommended age-related stimulation adjustments based on age-related changes seen in vagus nerve characteristics. Early studies indicated that children might respond more rapidly than adults would, with reductions in the interval between stimulations resulting in improved control [39, 48, 58]. Additional pediatric studies reported that higher output currents might be required, particularly when lower pulse durations are used [73–75]. Optimal stimulus parameter settings for patients of various ages or with specific seizure types or syndromes, however, have not been defined yet.

Table 1c
Aspire SR (Model 106) and SenTiva (Model 1000) parameters and suggested therapeutic values and AutoStim features.

Parameter	Units	Suggested settings
Tachycardia detection	ON/OFF	ON
Heartbeat detection (sensitivity)	1–5	3
Threshold for AutoStim	20–70%	20–40%
Verify heartbeat detection		
AutoStim mode settings		
Output current	Milliamps	1.50–2.25
Pulse width	Microseconds	250
ON—time	Seconds	30

AutoStim current is the same as or 0.125 mA above normal output (and ALWAYS < magnet output).

Table 1d
SenTiva (Model 1000) features.

- Wireless wand (can be used with wire)
- New tablet and screen format (can be used with older VNS models)
- All the features of Aspire SR (Model 106) plus:
  - Guided programming
  - Day–night programming
  - Low heart rate threshold (tracks if this occurs after Magnet or AutoStim)
  - Prone position detection (tracks if this occurs after Magnet or AutoStim)
  - Scheduled programming parameters (up to 7 steps, one every 1–4 weeks, suggested increase is 0.125 mA every 2 weeks)
  - Event and trend monitoring
  - VNS therapy session report

Please cite this article as: Wheless JW, et al, Vagus nerve stimulation (VNS) therapy update, Epilepsy Behav (2018), https://doi.org/10.1016/j.yebeh.2018.06.032

Fig. 3. VNS therapy generators: Models 103, 104, 105, and 106.

3. Complications and adverse effects

Vagus nerve stimulation therapy is safe and, in general, well tolerated. Adverse events are related either to the surgical procedure or to the electrical stimulation itself.

Surgical complications and difficulties are rare. Incisional infections are unusual and generally respond to antibiotic therapy. Fluid accumulation at the generator site with or without infection occurs in 1% to 2% of implantations and resolves with aspiration and antibiotics; the rare cases of refractory infection require removal of the generator. Unilateral vocal cord paralysis, which accompanies approximately 1% of implants, may be caused by excess manipulation of the vagus nerve and subsequent damage to the vagal artery and its reinforcing arterioles [76]; in most cases, it remits completely over several weeks. Proper selection of the correct lead wire size may minimize this complication as it occurs twice as often when the lead with a coil diameter of 2 mm (vs. 3 mm) was used in patients over 18 years of age [77]. Lead wire fracture secondary to trauma is rare.

Common side effects, which occur primarily when the stimulator is actually delivering a pulse (Table 5), are dose-dependent and usually mild or absent when VNS parameters are appropriately programmed [23, 78, 79]; many patients become accustomed to them with time. Initiating therapy at 20 Hz with a pulse width of 250 s dramatically improves device tolerability, which is now the recommended initial stimulator setting. Stimulation-related adverse events include voice alteration, cough, dyspnea, paresthesia, headache, and local pain. The frequency of these adverse events decreases over time with ongoing treatment. Many patients experience hoarseness or a change in vocal quality and tingling over the left cervical region on delivery of the electrical pulse. Subjective dyspnea or a sensation of muscle tightening in the neck may occur, without changes on pulmonary function testing [23]. Cough or throat pain during stimulus delivery sometimes necessitates a reduction in current [80].

Children with a history of dysphagia may experience swallowing difficulties during VNS therapy [81, 82]; adjusting the device settings or using a magnet to turn off the stimulator during mealtime may help. The majority of side effects, including many of the rare incidents reported, are amenable to stimulus modifications, which could include changes in output current and/or pulse width.

3.1. Impact on sleep apnea syndrome

Vagus nerve stimulation might have an unfavorable impact on sleep breathing disorders (SBD). In a prospective series of 23 adult patients with epilepsy undergoing VNS therapy, 57.9% of patients with lack of previous obstructive sleep apnea (OSA) syndrome developed new-onset mild to moderate SBD while 50% of those with preexisting OSA worsened their apneas [83]. In another series of 18 adults who systematically underwent sleep polygraphy or polysomnography before and after vagus nerve stimulator implantation, 4 patients without preexisting SBD

Fig. 4. SenTiva (Model 1000): wireless programming wand, tablet, and device.

Please cite this article as: Wheless JW, et al, Vagus nerve stimulation (VNS) therapy update, Epilepsy Behav (2018), https://doi.org/10.1016/j.yebeh.2018.06.032

Table 2
Efficacy of VNS therapy in clinical studies.

Study	Design	Seizure type	Patients (no.)	Patient age (years)	Year of first implant	Patients with >50% response (%)	Mean reduction in seizures/day (%)
E01	Pilot, longitudinal	Partial	11	20–58	1998	30	24[a]
E02	Pilot, longitudinal	Partial	5	18–42	1990	50	40
E04	Open, longitudinal	All types	124	3–63	1990	29	7[a]
E03	Randomized, parallel, high/low	Partial	115	13–57	1991	31/14	24[a]/6
E05	Randomized, parallel, high/low	Partial	198	13–60	1995	23/16	28[b]/15[b]

[a] $p \leq 0.05$, by Student *t*-test.
[b] $p < 0.0001$, by analysis of variance.

developed OSA after VNS therapy was initiated, while the condition of 1 of the 2 patients with preexisting OSA worsened [84]. All 5 patients were successfully treated with combinations of continuous positive airway pressure, positional therapy, or VNS parameter modification. Initiating VNS therapy with a frequency of 20 Hz and a pulse width of 250 μs dramatically reduces the risk of exacerbating a SBD.

4. Impact on mortality and sudden unexpected death in epilepsy (SUDEP)

The impact of VNS on mortality and SUDEP remains unsettled, with some data suggesting that it might reduce the risk of SUDEP. The US VNS database, which included more than 40,000 patients between 1988 and 2012, was used to investigate the SUDEP rate as a function of the duration of VNS therapy [85]. The cohort included 277,661 person-years of follow-up and 3689 deaths, including 632 SUDEP. Significantly lower SUDEP rates were observed during years 3–10 of follow-up as compared with years 1–2 (rate ratio, 0.68; 95% confidence interval, 0.53–0.87; $p = 0.002$). While this finding is consistent with that of a previous small-scale study [86], several factors other than VNS therapy could account for this finding, including the natural evolution of SUDEP rates over the years. Furthermore, another small-scale study failed to find difference in SUDEP rate as a function of VNS therapy duration [87].

5. Cost analysis

Vagus nerve stimulation is an empiric therapy with no way to predict response except by trial. The initial cost (often between $15,000 and $25,000) can be prohibitive without coverage by a third-party payer. Over the life of the system, however, this cost approximates that of many of the new AEDs [88]. Moreover, although weeks to months may elapse before seizure frequency decreases, cost-effectiveness studies indicate that VNS therapy provides a substantial cost-savings benefit to healthcare systems over the long-term course of treatment [89, 90]. These cost benefits are sustained over time and are sufficient to cover or exceed the cost of the device. Further savings can be seen in significant reductions in healthcare utilization and time spent on epilepsy-related matters with VNS therapy over time. One study looked at healthcare utilization of 138 patients with refractory epilepsy, comparing 1 year of baseline data followed by 4 years of quarterly follow-up data with VNS therapy [91]. The results showed significant reductions in the numbers of emergency department visits (99% decrease), hospitalizations (70% decrease), and hospital lengths of stay (67% decrease) beginning with the first quarter after vagus nerve stimulator implantation and therapy ($p < 0.05$ for all postimplantation quarters). A 91% decrease was also seen in outpatient visits following VNS therapy, and significant decreases were seen for the average number of patients who could not work because of health-related concerns ($p = 0.002$) and the average time spent caring for health problems ($p < 0.001$). These benefits resulting from VNS therapy—in addition to healthcare utilization savings—further reflect positive changes in QoL for both patients and their caregivers. In a US study evaluating the long-term medical and economic benefits of VNS therapy using Medicaid data from 5 states ($n = 1655$), VNS therapy was associated with lower average healthcare costs and epilepsy-related clinical events [92]. Hospitalizations, emergency room visits, and outpatient visits all were significantly reduced during the post-VNS period compared with the pre-VNS period ($p < 0.0001$). Serious events—such as grand mal status, fractures, and traumatic head injuries—were also reduced in the post-VNS period. Despite the initial expense of VNS therapy, the reductions in healthcare utilization and epilepsy events resulted in a net cost-savings for VNS therapy after 1.5 years of treatment.

6. Selection of candidates

In the United States, VNS therapy is indicated as an adjunctive treatment for adults and adolescents 4 years of age or older with refractory partial-onset seizures [21]. In the European Union, VNS therapy is indicated as an adjunctive treatment for patients with partial or generalized-onset seizures without an age limitation. However, indications for VNS therapy were derived from the clinical trial experience, not from an understanding of its physiologic action. Age, sex, seizure type or syndrome, etiology, frequency of seizures, or interictal epileptiform discharges do not predict response to VNS therapy. The type or number of coadministered AEDs also does not predict response [63, 93]. However, many studies show favorable outcomes in many of these populations although complete seizure freedom is rarely achieved [69]. A recent study also indicated that VNS therapy should be considered in patients with posttraumatic epilepsy, which is often resistant to AED therapy and not often amenable to epilepsy surgery [94].

In October 2013, the American Academy of Neurology updated the evidence-based VNS therapy guidelines for the treatment of epilepsy [95] (Table 6). The updated guidelines provide an update on data regarding the efficacy and safety of VNS therapy for epilepsy since publication of the original guidelines in 1999. Previous guidelines did not provide guidance on many of the patients with epilepsy populations

Table 3
Pediatric epilepsies and epilepsy syndromes responsive to VNS therapy.

A. Seizure types	Focal onset
	Focal to bilateral tonic–clonic
	Generalized onset (absence, atonic, tonic–clonic, clonic, tonic)
B. Epilepsy syndromes	Dravet syndrome
	Lennox–Gastaut syndrome
	Childhood absence epilepsy
	Juvenile absence epilepsy
	Juvenile myoclonic epilepsy
	Genetic generalized epilepsies

Table 4
Comorbidities and etiologies to consider when using VNS therapy.

A. Comorbidities	Depression
	Partial adherence to medication
	Frequent emergency department visits (for seizures)
B. Etiologies	Ring chromosome 20
	Tuberous sclerosis complex
	Posttraumatic epilepsy
	Lafora body disease
	Unverricht–Lundborg disease

Please cite this article as: Wheless JW, et al, Vagus nerve stimulation (VNS) therapy update, Epilepsy Behav (2018), https://doi.org/10.1016/j.yebeh.2018.06.032

Table 5
Adverse events with vagus nerve stimulation.[a]

Adverse event	No. of patients (%)	
	E03 and E05 patients (n = 314; 591 device years) > 3 months of follow-up	E03 and E05 patients with high stimulation (n = 152) > 3 months of follow-up
Voice alteration	156 (50)	91 (60)
Increased coughing	129 (41)	57 (38)
Paresthesia	87 (28)	32 (21)
Dyspnea	55 (18)	32 (21)
Dyspepsia	36 (12)	22 (15)
Laryngismus	10 (3.2)	9 (5.9)

[a] Number of patients reporting the adverse event at least once in the E03 and E05 randomized studies.

in which VNS therapy is actively being used. The literature review found 1274 manuscripts for VNS therapy since the last review. Of these, 216 articles were reviewed to answer 8 clinical questions, summarized in Table 3. The clinical evidence supports the use of VNS therapy across a range of populations with refractory epilepsy, and the impact of the reviewed studies (with specific focus on the intensity and magnitude of the responses) continues to be supportive.

Although optimal use parameters continue to be defined, candidates should meet the following criteria: (1) medically refractory seizures; (2) adequate trials of at least 2 AEDs; (3) exclusion of nonepileptic events; and (4) ineligibility for epilepsy surgery (Figs. 5, 6). Focal resective surgery (i.e., temporal lobectomy or lesional neocortical epilepsy) is preferred in appropriate patients because of its superior seizure-freedom rate [96–98]. Unless the patient is at risk for memory decline, at risk for significant impairment in language function, or adverse to epilepsy surgery, focal resection should be performed in patients with a single focus in the noneloquent cortex. Recent open studies suggest that VNS therapy may be used among patients considered for corpus callosotomy, producing lower rates of morbidity [99–102], and for patients who have a prior corpus callosotomy and among those who have previously undergone epilepsy surgery [30, 103–105]. A study of 376 patients (110 of whom had at least 1 failed craniotomy before VNS and 266 with no history of intracranial epilepsy surgery before VNS) showed no significant difference in the mean percentage seizure reduction between patients with and without a history of epilepsy surgery (59% vs. 57%; p = 0.42) [105]. Earlier use (i.e., within 2 years of seizure onset or after failure of 2 or 3 AEDs) of VNS therapy may also produce a higher response rate and reduce the negative side effects associated with long-term epilepsy and AED therapy, which hinder development [29, 92, 106, 107]. Patients with a history of nonadherence to their AED regimens, particularly those on polypharmacy, may also be good candidates for VNS therapy because of the assured compliance and lack of further drug–drug interactions with VNS therapy [108, 109]. Additional considerations to use VNS include patients who have a comorbid mood disorder or frequent emergency room visits or hospitalizations secondary to poorly controlled seizures.

7. Future developments

Vagus nerve stimulation therapy was the first device approved for the treatment of epilepsy and its success has raised interest in the role of neurostimulation as a treatment for refractory epilepsy. Since the first device implantation about 30 years ago, the number of AEDs has increased; yet, uncontrolled seizures continue. The codification of refractory epilepsy by the International League Against Epilepsy (ILAE) in 2010 [110] increased visibility around the need for nonpharmacologic treatment options earlier in the course of the disease rather than waiting until multiple medications have failed and surgery is not an option.

Advances in VNS technology provide seizure detection based on heart rate changes. As the vast majority of refractory epilepsies are associated with ictal tachycardia, this allows rapid changes in heart rate to be used as a surrogate marker for seizure onset (and converts standard VNS therapy from an open-loop form of stimulation to a closed-loop based on ictal tachycardia detection) [111, 112]. In addition, a review of the literature indicates additional benefits from on-demand magnet mode stimulation [113]. These two observations have led to changes in VNS technology and the newest models to incorporate these and other features into the device software. The AspireSR (Model 106) [114–117] and SenTiva (Model 1000) devices detect ictal tachycardia and then deliver a timed therapy dose to prevent seizure progression and abort the seizure. Additional data collected by the Model 1000 device include detections occurring in the prone position that were associated with bradycardia, which can potentially allow the physician to put individual patient strategies in place to lower SUDEP risk.

Future real-world studies may demonstrate that the use of one form of neurostimulation does not preclude the use of an additional form of neurostimulation for seizure control, given the distinct mechanisms of

Table 6
Summary of AAN updated evidence-based guidelines for VNS therapy.

Clinical question	Recommendation/clinical context
Is VNS therapy beneficial in children with epilepsy?	VNS therapy may be considered as adjunctive treatment for children with partial or generalized epilepsy.[a]
Is VNS therapy beneficial in patients with Lennox-Gastaut syndrome (LGS)?	VNS therapy may be considered in patients with LGS.[a]
Is VNS therapy associated with mood improvement in patients with epilepsy?	In adult patients receiving VNS therapy for epilepsy, improvement in mood may be an additional benefit.[a]
Is VNS therapy associated with reduced seizure frequency over time?	VNS therapy may be considered progressively effective in patients over multiple years of exposure.[a]
Does rapid cycling[b] improve seizure frequency more often than do standard stimulation settings?	Optimal VNS therapy settings are still unknown. The evidence is insufficient to support a recommendation for the use of standard stimulation vs. rapid stimulation.
Does using additional magnet-activated stimulation trains for auras or at seizure onset interrupt seizures?	VNS therapy magnet activation may be associated with seizure abortion when used at the time of seizure auras.[a] Seizure abortion with magnet use may be associated with overall response to VNS treatment.[b]
Have new safety concerns emerged since the last VNS therapy assessment?	No new safety concerns were identified. The rates of sudden unexpected death in epilepsy (SUDEP) dropped in the first 2 years of VNS therapy.
Do adverse effects differ among children and adults?	Children may have greater risk for wound infection than adults because of behaviors more commonly found in children. Extra vigilance in monitoring for occurrence of site infection in children should be undertaken.

[a] Based on data from class III studies; U, unproven, data inadequate, or conflicting.
[b] Rapid cycling has shorter on times and off times, typically 7 s ON and 30 s OFF, compared with standard settings, typically 30 s ON and 5 min OFF.

Please cite this article as: Wheless JW, et al, Vagus nerve stimulation (VNS) therapy update, Epilepsy Behav (2018), https://doi.org/10.1016/j.yebeh.2018.06.032

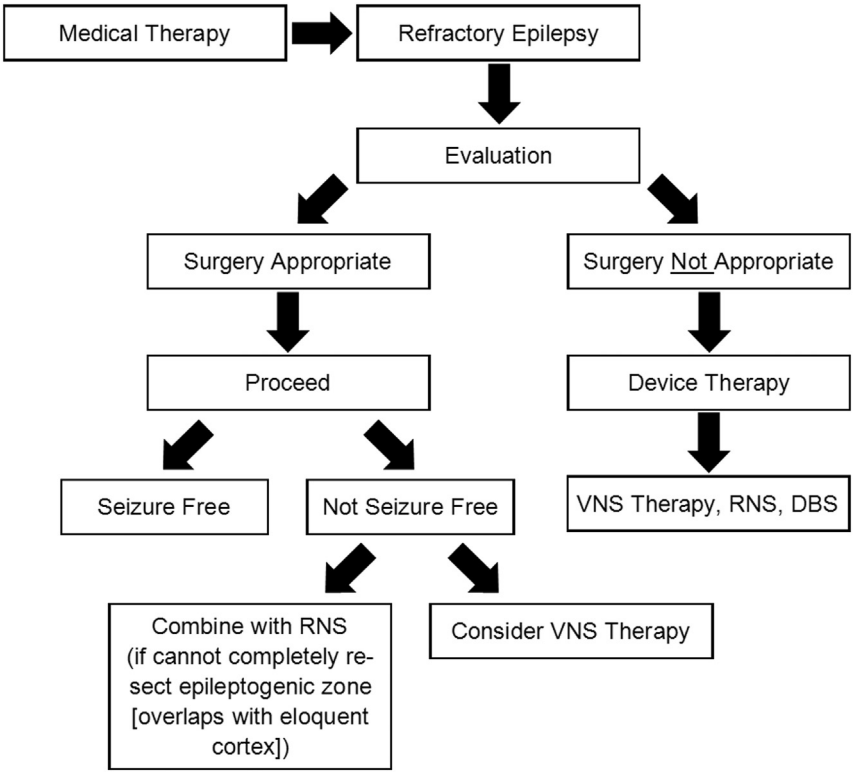

Fig. 5. Epilepsy: treatment sequence for epilepsy surgery and devices. Options for pharmacoresistant epilepsy. If surgery is appropriate and there are minimal risks (i.e., memory, language, etc.), we would suggest the patient pursue that treatment. If surgery is not appropriate, then device therapy is an option (several factors influence options here — see Fig. 6).

seizure control each possesses. This same principle probably applies to failure to respond to one form of neurostimulation.

8. Conclusion

Vagus nerve stimulation therapy launched the modern era of neurostimulation, and it continues to be the most commonly used form of neurostimulation to treat epilepsy. Now, 30 years after the first patients were treated with the vagus nerve stimulator, multiple studies have continued to support its effectiveness for multiple seizure types and epilepsy syndromes, a predictable and benign side-effect profile, and QoL benefits to the patient. In light of these benefits, it is incumbent for the practicing epileptologist and neurologist to be comfortable with patient selection for VNS therapy, the use of the device, and the expected outcome. Further advances in electronics and technology will ensure this device continues to be part of the armamentarium every epileptologist uses to treat epilepsy across the age spectrum.

Conflicts of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Philippe Ryvlin received speaker and consultant fees from LivaNova. Andrew Gienapp has no financial interests to declare. James Wheless is a consultant for Eisai, GW Pharma, Lundbeck, NeuroPace, Sun, Supernus, and Upsher–Smith; received grants from Eisai, GW Pharma, INSYS Inc., LivaNova,

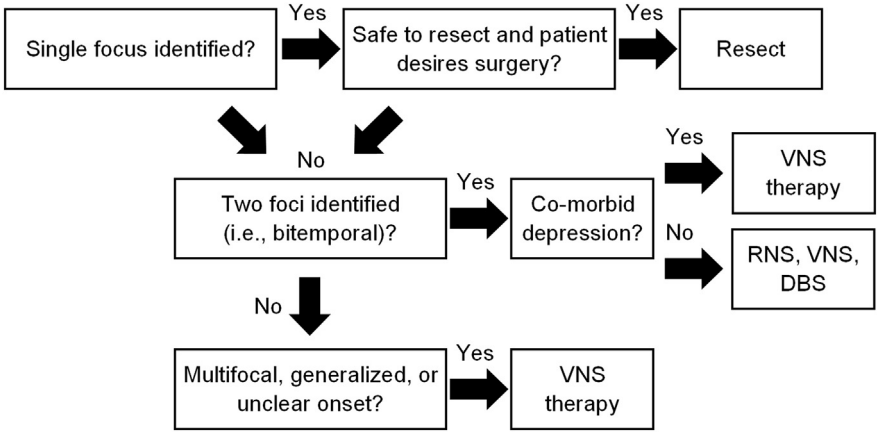

Fig. 6. Device therapy options. Comorbidities, invasiveness of device, and seizure focus determine which device may be used initially (some patients may benefit from more than one device).

Lundbeck, Mallinckrodt, Neuralis, NeuroPace, Shainberg Foundation, Upsher–Smith, and Zogenix; and serves on the speaker's bureaus of Eisai, LivaNova, Lundbeck, Mallinckrodt, Supernus, and Upsher–Smith.

Addendum

Videotapes and information on the VNS therapy system are available free to patients, nurses, and physicians from LivaNova, Inc. (www.livanova.com).

References

[1] Brodie MJ. Road to refractory epilepsy: the Glasgow story. Epilepsia 2013;54(Suppl. 2):5–8.
[2] Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol 2018;75:279–86.
[3] Schmidt D. The clinical impact of new antiepileptic drugs after a decade of use in epilepsy. Epilepsy Res 2002;50:21–32.
[4] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000; 342:314–9.
[5] Mohanraj R, Brodie MJ. Diagnosing refractory epilepsy: response to sequential treatment schedules. Eur J Neurol 2006;13:277–82.
[6] Hitiris N, Mohanraj R, Norrie J, Sills GJ, Brodie MJ. Predictors of pharmacoresistant epilepsy. Epilepsy Res 2007;75:192–6.
[7] Jallon P. The problem of intractability: the continuing need for new medical therapies in epilepsy. Epilepsia 1997;38(Suppl. 9):S37–42.
[8] Patsalos PN, Duncan JS. Antiepileptic drugs. A review of clinically significant drug interactions. Drug Saf 1993;9:156–84.
[9] Pellock JM, Pippenger CE. Adverse effects of antiepileptic drugs. In: Dodson WE, Pellock JM, editors. Pediatric epilepsy: diagnosis and therapy. New York: Demos; 1993. p. 253–64.
[10] Schmidt D. Adverse effects of antiepileptic drugs. New York: Raven Press; 1982.
[11] Pellock JM. Antiepileptic drug therapy in the United States: a review of clinical studies and unmet needs. Neurology 1995;45:S17–24.
[12] Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. Epilepsia 2001;42: 1255–60.
[13] Camfield P, Camfield C. Acute and chronic toxicity of antiepileptic medications: a selective review. Can J Neurol Sci 1994;21:S7–11.
[14] Faught E, Duh MS, Weiner JR, Guerin A, Cunnington MC. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM study. Neurology 2008;71:1572–8.
[15] Wheless JW, Ashwal S. The ketogenic diet. In: Swaiman KF, Ashwal S, editors. Pediatric neurology: principles and practice. Philadelphia, PA: CV Mosby Co.; 1999. p. 719–28.
[16] Vining EP, Freeman JM, Ballaban-Gil K, Camfield CS, Camfield PR, Holmes GL, et al. A multicenter study of the efficacy of the ketogenic diet. Arch Neurol 1998;55: 1433–7.
[17] Epilepsy Foundation. Epilepsy: a report to the nation. Landover, MD: Epilepsy Foundation of America; 1999.
[18] Wheless JW. Intractable epilepsy: a survey of patients and caregivers. Epilepsy Behav 2006;8:756–64.
[19] Fisher RS, Parks-Trusz SL, Lehman C. Social issues in epilepsy. In: Shorvon S, Dreifuss F, Fish D, Thomas D, editors. The treatment of epilepsy. Cambridge, MA: Blackwell Science; 1996. p. 357–69.
[20] Schachter SC, Saper CB. Vagus nerve stimulation. Epilepsia 1998;39:677–86.
[21] LivaNova. VNS therapy system physician's manual. London, UK: LivaNova; 2018.
[22] Ben-Menachem E, Manon-Espaillat R, Ristanovic R, Wilder BJ, Stefan H, Mirza W, et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. Epilepsia 1994;35:616–26.
[23] Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998;51:48–55.
[24] Ryvlin P, Gilliam FG, Nguyen DK, Colicchio G, Iudice A, Tinuper P, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (open prospective randomized long-term effectiveness) trial. Epilepsia 2014;55:893–900.
[25] Englot DJ, Hassnain KH, Rolston JD, Harward SC, Sinha SR, Haglund MM. Quality-of-life metrics with vagus nerve stimulation for epilepsy from provider survey data. Epilepsy Behav 2017;66:4–9.
[26] Kawai K, Tanaka T, Baba H, Bunker M, Ikeda A, Inoue Y, et al. Outcome of vagus nerve stimulation for drug-resistant epilepsy: the first three years of a prospective Japanese registry. Epileptic Disord 2017;19:327–38.
[27] Garcia-Pallero MA, Garcia-Navarrete E, Torres CV, Pastor J, Navas M, Sola RG. Effectiveness of vagal nerve stimulation in medication-resistant epilepsy. Comparison between patients with and without medication changes. Acta Neurochir 2017; 159:131–6.
[28] Hilderink J, Tjepkema-Cloostermans MC, Geertsema A, Glastra-Zwiers J, de Vos CC. Predicting success of vagus nerve stimulation (VNS) from EEG symmetry. Seizure 2017;48:69–73.
[29] Elliott RE, Rodgers SD, Bassani L, Morsi A, Geller EB, Carlson C, et al. Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases. J Neurosurg Pediatr 2011;7:491–500.
[30] Helmers SL, Wheless JW, Frost M, Gates J, Levisohn P, Tardo C, et al. Vagus nerve stimulation therapy in pediatric patients with refractory epilepsy: retrospective study. J Child Neurol 2001;16:843–8.
[31] Alexopoulos AV, Kotagal P, Loddenkemper T, Hammel J, Bingaman WE. Long-term results with vagus nerve stimulation in children with pharmacoresistant epilepsy. Seizure 2006;15:491–503.
[32] Benifla M, Rutka JT, Logan W, Donner EJ. Vagal nerve stimulation for refractory epilepsy in children: indications and experience at The Hospital for Sick Children. Childs Nerv Syst 2006;22:1018–26.
[33] You SJ, Kang HC, Kim HD, Ko TS, Kim DS, Hwang YS, et al. Vagus nerve stimulation in intractable childhood epilepsy: a Korean multicenter experience. J Korean Med Sci 2007;22:442–5.
[34] Cersosimo RO, Bartuluchi M, Fortini S, Soraru A, Pomata H, Caraballo RH. Vagus nerve stimulation: effectiveness and tolerability in 64 paediatric patients with refractory epilepsies. Epileptic Disord 2011;13:382–8.
[35] Connor Jr DE, Nixon M, Nanda A, Guthikonda B. Vagal nerve stimulation for the treatment of medically refractory epilepsy: a review of the current literature. Neurosurg Focus 2012;32:E12.
[36] Frost M, Gates J, Helmers SL, Wheless JW, Levisohn P, Tardo C, et al. Vagus nerve stimulation in children with refractory seizures associated with Lennox–Gastaut syndrome. Epilepsia 2001;42:1148–52.
[37] Parker AP, Polkey CE, Binnie CD, Madigan C, Ferrie CD, Robinson RO. Vagal nerve stimulation in epileptic encephalopathies. Pediatrics 1999;103:778–82.
[38] Lundgren J, Amark P, Blennow G, Stromblad LG, Wallstedt L. Vagus nerve stimulation in 16 children with refractory epilepsy. Epilepsia 1998;39:809–13.
[39] Hornig GW, Murphy JV, Schallert G, Tilton C. Left vagus nerve stimulation in children with refractory epilepsy: an update. South Med J 1997;90:484–8.
[40] Parain D, Penniello MJ, Berquen P, Delangre T, Billard C, Murphy JV. Vagal nerve stimulation in tuberous sclerosis complex patients. Pediatr Neurol 2001; 25:213–6.
[41] Parker AP, Polkey CE, Robinson RO. Vagal nerve stimulation in the epileptic encephalopathies: 3-year follow-up. Pediatrics 2001;108:221.
[42] Murphy JV, Wheless JW, Schmoll CM. Left vagal nerve stimulation in six patients with hypothalamic hamartomas. Pediatr Neurol 2000;23:167–8.
[43] Hosain S, Nikalov B, Harden C, Li M, Fraser R, Labar D. Vagus nerve stimulation treatment for Lennox–Gastaut syndrome. J Child Neurol 2000;15:509–12.
[44] Aicardi J. Vagal nerve stimulation in epileptic encephalopathies. Pediatrics 1999; 103:821–2.
[45] Aldenkamp AP, Majoie HJ, Berfelo MW, Evers SM, Kessels AG, Renier WO, et al. Long-term effects of 24-month treatment with vagus nerve stimulation on behaviour in children with Lennox–Gastaut syndrome. Epilepsy Behav 2002;3:475–9.
[46] Wilfong AA, Schultz RJ. Vagus nerve stimulation for treatment of epilepsy in Rett syndrome. Dev Med Child Neurol 2006;48:683–6.
[47] Zamponi N, Rychlicki F, Corpaci L, Cesaroni E, Trignani R. Vagus nerve stimulation (VNS) is effective in treating catastrophic 1 epilepsy in very young children. Neurosurg Rev 2008;31:291–7.
[48] Rossignol E, Lortie A, Thomas T, Bouthiller A, Scavarda D, Mercier C, et al. Vagus nerve stimulation in pediatric epileptic syndromes. Seizure 2009;18:34–7.
[49] Major P, Thiele EA. Vagus nerve stimulation for intractable epilepsy in tuberous sclerosis complex. Epilepsy Behav 2008;13:357–60.
[50] Koenig SA, Longin E, Bell N, Reinhard J, Gerstner T. Vagus nerve stimulation improves severely impaired heart rate variability in a patient with Lennox–Gastaut-Syndrome. Seizure 2008;17:469–72.
[51] You SJ, Kang HC, Ko TS, Kim HD, Yum MS, Hwang YS, et al. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox–Gastaut syndrome. Brain and Development 2008;30:195–9.
[52] Zamponi N, Passamonti C, Cappanera S, Petrelli C. Clinical course of young patients with Dravet syndrome after vagal nerve stimulation. Eur J Paediatr Neurol 2011; 15:8–14.
[53] Fulton SP, Van Poppel K, McGregor AL, Mudigoudar B, Wheless JW. Vagus nerve stimulation in intractable epilepsy associated with SCN1A gene abnormalities. J Child Neurol 2017;32:494–8.
[54] Dibue-Adjei M, Fischer I, Steiger HJ, Kamp MA. Efficacy of adjunctive vagus nerve stimulation in patients with Dravet syndrome: a meta-analysis of 68 patients. Seizure 2017;50:147–52.
[55] Murphy JV. Left vagal nerve stimulation in children with medically refractory epilepsy. The pediatric VNS study group. J Pediatr 1999;134:563–6.
[56] Hornig G, Murphy JV. Vagal nerve stimulation: updated experience in 60 pediatric patients [abstract]. AES Proceedings, Annual Meeting of the American Epilepsy Society, San Diego, CA, December 6–9, 1998, vol. 39. Epilepsia; 1998. p. 169.
[57] Schallert G, Murphy J. Vagal nerve stimulation: experience in 60 children [poster abstract]. Neurology 1998;50:14.
[58] Murphy JV, Hornig G, Schallert G. Left vagal nerve stimulation in children with refractory epilepsy. Preliminary observations. Arch Neurol 1995;52:886–9.
[59] Park YD. The effects of vagus nerve stimulation therapy on patients with intractable seizures and either Landau–Kleffner syndrome or autism. Epilepsy Behav 2003;4: 286–90.
[60] Gates J, Huf R, Frost M. Vagus nerve stimulation for patients in residential treatment facilities. Epilepsy Behav 2001;2:563–7.
[61] Andriola MR, Vitale SA. Vagus nerve stimulation in the developmentally disabled. Epilepsy Behav 2001;2:129–34.
[62] Winston KR, Levisohn P, Miller BR, Freeman J. Vagal nerve stimulation for status epilepticus. Pediatr Neurosurg 2001;34:190–2.

Please cite this article as: Wheless JW, et al, Vagus nerve stimulation (VNS) therapy update, Epilepsy Behav (2018), https://doi.org/10.1016/j.yebeh.2018.06.032

[63] Labar D, Murphy J, Tecoma E. Vagus nerve stimulation for medication-resistant generalized epilepsy. E04 VNS study group. Neurology 1999;52:1510–2.
[64] Ng M, Devinsky O. Vagus nerve stimulation for refractory idiopathic generalised epilepsy. Seizure 2004;13:176–8.
[65] Holmes MD, Silbergeld DL, Drouhard D, Wilensky AJ, Ojemann LM. Effect of vagus nerve stimulation on adults with pharmacoresistant generalized epilepsy syndromes. Seizure 2004;13:340–5.
[66] Nei M, O'Connor M, Liporace J, Sperling MR. Refractory generalized seizures: response to corpus callosotomy and vagal nerve stimulation. Epilepsia 2006;47:115–22.
[67] Kostov H, Larsson PG, Roste GK. Is vagus nerve stimulation a treatment option for patients with drug-resistant idiopathic generalized epilepsy? Acta Neurol Scand Suppl 2007;187:55–8.
[68] Labar D, Nikolov B, Tarver B, Fraser R. Vagus nerve stimulation for symptomatic generalized epilepsy: a pilot study. Epilepsia 1998;39:201–5.
[69] Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. J Neurosurg 2011;115:1248–55.
[70] Arya R, Greiner HM, Lewis A, Mangano FT, Gonsalves C, Holland KD, et al. Vagus nerve stimulation for medically refractory absence epilepsy. Seizure 2013;22:267–70.
[71] Englot DJ, Rolston JD, Wright CW, Hassnain KH, Chang EF. Rates and predictors of seizure freedom with vagus nerve stimulation for intractable epilepsy. Neurosurgery 2016;79:345–53.
[72] Koo B, Ham SD, Sood S, Tarver B. Human vagus nerve electrophysiology: a guide to vagus nerve stimulation parameters. J Clin Neurophysiol 2001;18:429–33.
[73] Majoie HJ, Berfelo MW, Aldenkamp AP, Evers SM, Kessels AG, Renier WO. Vagus nerve stimulation in children with therapy-resistant epilepsy diagnosed as Lennox–Gastaut syndrome: clinical results, neuropsychological effects, and cost-effectiveness. J Clin Neurophysiol 2001;18:419–28.
[74] Crumrine PK. Vagal nerve stimulation in children. Semin Pediatr Neurol 2000;7:216–23.
[75] Heck C, Helmers SL, DeGiorgio CM. Vagus nerve stimulation therapy, epilepsy, and device parameters: scientific basis and recommendations for use. Neurology 2002;59:S31–7.
[76] Fernando DA, Lord RS. The blood supply of vagus nerve in the human: its implication in carotid endarterectomy, thyroidectomy and carotid arch aneurectomy. Ann Anat 1994;176:333–7.
[77] Robinson LC, Winston KR. Relationship of vocal cord paralysis to the coil diameter of vagus nerve stimulator leads. J Neurosurg 2015;122:532–5.
[78] A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures The Vagus Nerve Stimulation Study Group, Neurology 1995;45:224–30.
[79] Ramsay RE, Uthman BM, Augustinsson LE, Upton AR, Naritoku D, Willis J, et al. Vagus nerve stimulation for treatment of partial seizures: 2. Safety, side effects, and tolerability. First International Vagus Nerve Stimulation Study Group. Epilepsia 1994;35:627–36.
[80] Liporace J, Hucko D, Morrow R, Barolat G, Nei M, Schnur J, et al. Vagal nerve stimulation: adjustments to reduce painful side effects. Neurology 2001;57:885–6.
[81] Lundgren J, Ekberg O, Olsson R. Aspiration: a potential complication to vagus nerve stimulation. Epilepsia 1998;39:998–1000.
[82] Schallert G, Foster J, Lindquist N, Murphy JV. Chronic stimulation of the left vagal nerve in children: effect on swallowing. Epilepsia 1998;39:1113–4.
[83] Zambrelli E, Saibene AM, Furia F, Chiesa V, Vignoli A, Pipolo C, et al. Laryngeal motility alteration: a missing link between sleep apnea and vagus nerve stimulation for epilepsy. Epilepsia 2016;57:e24–7.
[84] Salvade A, Ryvlin P, Rossetti AO. Impact of vagus nerve stimulation on sleep-related breathing disorders in adults with epilepsy. Epilepsy Behav 2018;79:126–9.
[85] Ryvlin P, So EL, Gordon CM, Hesdorffer DC, Sperling MR, Devinsky O, et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. Epilepsia 2018;59:562–72.
[86] Annegers JF, Coan SP, Hauser WA, Leestma J. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. Epilepsia 2000;41:549–53.
[87] Granbichler CA, Nashef L, Selway R, Polkey CE. Mortality and SUDEP in epilepsy patients treated with vagus nerve stimulation. Epilepsia 2015;56:291–6.
[88] Graves N. Anticonvulsants: choices and costs. Am J Manag Care 1998;4:S463–4.
[89] Ben-Menachem E, Hellstrom K, Verstappen D. Analysis of direct hospital costs before and 18 months after treatment with vagus nerve stimulation therapy in 43 patients. Neurology 2002;59:S44–7.
[90] Boon P, D'Have M, Van Walleghem P, Michielsen G, Vonck K, Caemaert J, et al. Direct medical costs of refractory epilepsy incurred by three different treatment modalities: a prospective assessment. Epilepsia 2002;43:96–102.
[91] Bernstein AL, Hess T. Vagus nerve stimulation therapy for pharmacoresistant epilepsy: effect on healthcare utilization. Epilepsy Behav 2007;10:134–7.
[92] Helmers SL, Griesemer DA, Dean JC, Sanchez JD, Labar D, Murphy JV, et al. Observations on the use of vagus nerve stimulation earlier in the course of pharmacoresistant epilepsy: patients with seizures for six years or less. Neurologist 2003;9:160–4.
[93] Labar DR. Antiepileptic drug use during the first 12 months of vagus nerve stimulation therapy: a registry study. Neurology 2002;59:S38–43.
[94] Englot DJ, Rolston JD, Wang DD, Hassnain KH, Gordon CM, Chang EF. Efficacy of vagus nerve stimulation in posttraumatic versus nontraumatic epilepsy. J Neurosurg 2012;117:970–7.
[95] Morris III GL, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2013;81:1453–9.
[96] Van Ness PC. Surgical outcome for neocortical (extrahippocampal) focal epilepsy. In: Luders HO, editor. Epilepsy surgery. New York: Raven Press; 1992. p. 213–624.
[97] Sperling MR, O'Connor MJ, Saykin AJ, Plummer C. Temporal lobectomy for refractory epilepsy. JAMA 1996;276:470–5.
[98] Fisher RS, Handforth A. Reassessment: vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 1999;53:666–9.
[99] Baumgartner JE, Clifton GL, Wheless JW, Willmore LJ, Brookshire BL, Sorenson JM. Corpus callosotomy. Oper Tech Neurosurg 1995;1:45–51.
[100] Camfield PR, Camfield CS. Vagal nerve stimulation for treatment of children with epilepsy. J Pediatr 1999;134:532–3.
[101] Lancman G, Virk M, Shao H, Mazumdar M, Greenfield JP, Weinstein S, et al. Vagus nerve stimulation vs. corpus callosotomy in the treatment of Lennox–Gastaut syndrome: a meta-analysis. Seizure 2013;22:3–8.
[102] Sorenson JM, Wheless JW, Baumgartner JE, Thomas AB, Brookshire BL, Clifton GL, et al. Corpus callosotomy for medically intractable seizures. Pediatr Neurosurg 1997;27:260–7.
[103] Schwartz TH, Spencer DD. Strategies for reoperation after comprehensive epilepsy surgery. J Neurosurg 2001;95:615–23.
[104] Amar AP, Apuzzo ML, Liu CY. Vagus nerve stimulation therapy after failed cranial surgery for intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry. Neurosurgery 2004;55:1086–93.
[105] Elliott RE, Morsi A, Geller EB, Carlson CC, Devinsky O, Doyle WK. Impact of failed intracranial epilepsy surgery on the effectiveness of subsequent vagus nerve stimulation. Neurosurgery 2011;69:1210–7.
[106] Renfroe JB, Wheless JW. Earlier use of adjunctive vagus nerve stimulation therapy for refractory epilepsy. Neurology 2002;59:S26–30.
[107] Scherrmann J, Hoppe C, Kral T, Schramm J, Elger CE. Vagus nerve stimulation: clinical experience in a large patient series. J Clin Neurophysiol 2001;18:408–14.
[108] Helmers SL, Duh MS, Guerin A, Sarda SP, Samuelson TM, Bunker MT, et al. Clinical and economic impact of vagus nerve stimulation therapy in patients with drug-resistant epilepsy. Epilepsy Behav 2011;22:370–5.
[109] Helmers SL, Duh MS, Guerin A, Sarda SP, Samuelson TM, Bunker MT, et al. Clinical outcomes, quality of life, and costs associated with implantation of vagus nerve stimulation therapy in pediatric patients with drug-resistant epilepsy. Eur J Paediatr Neurol 2012;16:449–58.
[110] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069–77.
[111] Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: the head–heart connection. Seizure 2014;23:496–505.
[112] Hirsch M, Altenmuller DM, Schulze-Bonhage A. Latencies from intracranial seizure onset to ictal tachycardia: a comparison to surface EEG patterns and other clinical signs. Epilepsia 2015;56:1639–47.
[113] Fisher RS, Eggleston KS, Wright CW. Vagus nerve stimulation magnet activation for seizures: a critical review. Acta Neurol Scand 2015;131:1–8.
[114] Schneider UC, Bohlmann K, Vajkoczy P, Straub HB. Implantation of a new vagus nerve stimulation (VNS) therapy(R) generator, AspireSR(R): considerations and recommendations during implantation and replacement surgery—comparison to a traditional system. Acta Neurochir 2015;157:721–8.
[115] Fisher RS, Afra P, Macken M, Minecan DN, Bagic A, Benbadis SR, et al. Automatic vagus nerve stimulation triggered by ictal tachycardia: clinical outcomes and device performance—the U.S. E-37 trial. Neuromodulation 2016;19:188–95.
[116] Hampel KG, Vatter H, Elger CE, Surges R. Cardiac-based vagus nerve stimulation reduced seizure duration in a patient with refractory epilepsy. Seizure 2015;26:81–5.
[117] Boon P, Vonck K, van Rijckevorsel K, El Tahry R, Elger CE, Mullatti N, et al. A prospective, multicenter study of cardiac-based seizure detection to activate vagus nerve stimulation. Seizure 2015;32:52–61.

Please cite this article as: Wheless JW, et al, Vagus nerve stimulation (VNS) therapy update, Epilepsy Behav (2018), https://doi.org/10.1016/j.yebeh.2018.06.032