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REVIEW

The role of vagus nerve stimulation in refractory epilepsy

O papel da estimulação do nervo vago na epilepsia refratária

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ABSTRACT

Vagus nerve stimulation is an adjunctive therapy used to treat patients with refractory epilepsy who are not candidates for resective surgery or had poor results after surgical procedures. Its mechanism of action is not yet fully comprehended but it possibly involves modulation of the locus coeruleus, thalamus and limbic circuit through noradrenergic and serotonergic projections. There is sufficient evidence to support its use in patients with focal epilepsy and other seizure types. However, it should be recognized that improvement is not immediate and increases over time. The majority of adverse events is stimulation-related, temporary and decreases after adjustment of settings. Future perspectives to improve efficacy and reduce side effects, such as different approaches to increase battery life, transcutaneous stimulation and identification of prognostic factors, should be further investigated.

Keywords: vagus nerve stimulation; epilepsy.

RESUMO

A estimulação vagal é uma terapia paliativa utilizada no tratamento de pacientes com epilepsia refratária que não são candidatos à cirurgia ressectiva ou naqueles com evolução insatisfatória após o procedimento cirúrgico. Seu mecanismo de ação ainda não foi completamente elucidado mas possivelmente envolve a modulação do locus coeruleus, tálamo e circuito límbico através de projeções noradrenérgicas e serotoninérgicas. Atualmente há evidência suficiente para corroborar o uso desta terapia em pacientes com epilepsia focal e outros tipos de crise, com resultados que, apesar de não imediatos, melhoram progressivamente no longo prazo. Os eventos adversos são, em sua maioria, relacionados à estimulação e auto-limitados. Perspectivas futuras para aumentar a eficácia e reduzir os efeitos colaterais como a utilização de baterias com maior durabilidade, estimulação transcutânea e identificação de fatores prognósticos devem ser investigadas.

Palavras-chave: estimulação do nervo vago; epilepsia.

Epilepsy is one of the most common chronic neurologic diseases and affects at least 50 million people worldwide[1]. Although much has been understood about its causes, epilepsy is still extremely stigmatizing and many patients are victims of prejudice and social exclusion. The quality of life of those affected by the disease is remarkably compromised due to seizures, antiepileptic drugs (AED), cognitive impairment and physical limitations.

Those who do not achieve adequate seizure control, even with multiple AED trials, are considered refractory. Currently, medically resistant epilepsy is regarded as a worldwide health issue as it is endured by approximately one third of epileptic patients. The financial burden is substantial and, among all health costs of uncontrolled patients, nearly 50% are related to epilepsy care costs[2]. For these individuals, whose treatment is generally complex, epilepsy surgery may be indicated and can provide up to 80% seizure control, depending on distinct aspects such as time of follow-up and epileptic focus localization. Figure 1 illustrates the therapy options in epilepsy management.

One of the possible palliative options for patients who are not candidates for resective surgery is electrical vagus nerve stimulation (VNS). Although its mechanism of action has not been completely elucidated, it possibly involves diffuse cerebral metabolic changes, cortical and subcortical, through modulation of solitary tract nucleus and brainstem activities[3]. Its efficacy is related to reduction of both frequency and duration of seizures as well as improvement in quality of life[4].

This review aims to assess the main concepts involved in vagus nerve stimulation, from its anatomical principles and mechanisms of action to the recommendations regarding its indications, usual parameters and new trends.

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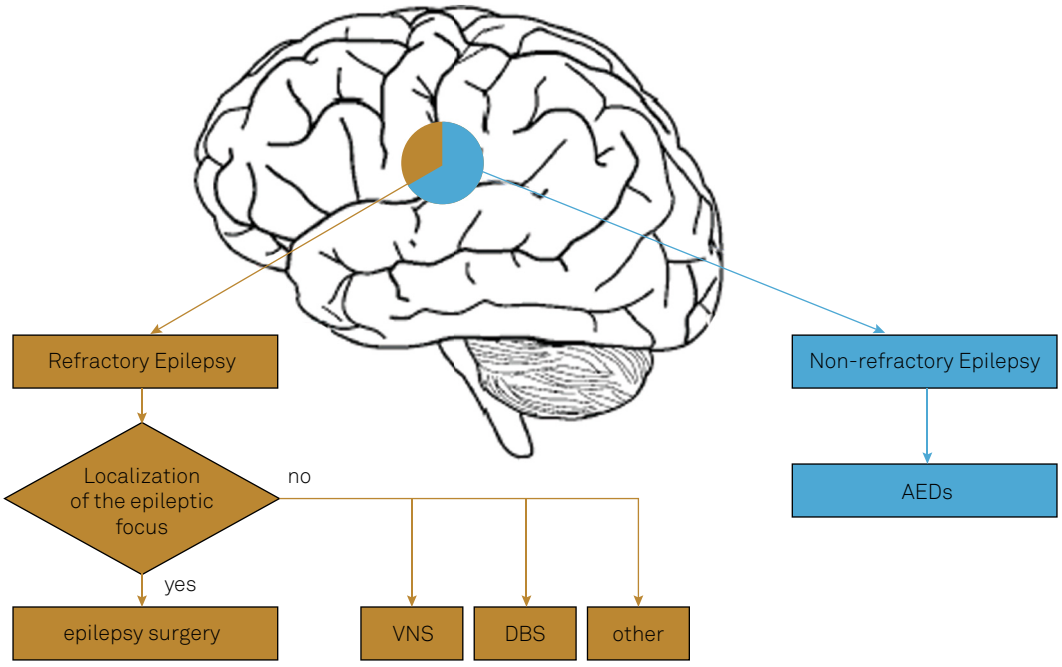

AEDs: antiepileptic drugs; DBS: deep brain stimulation; VNS: vagal nerve stimulation.
Figure 1. Diagram of therapy options in epilepsy management.

METHODS

A PubMed search was conducted for all English articles up to April 2017 using the terms "vagus OR vagal OR VNS AND epilepsy, which resulted in 1,394 papers. The query was then refined by inclusion of all review articles and prospective/retrospective clinical studies that evaluated VNS efficacy by seizure frequency for at least three months after implantation.

Historical aspects

Therapeutic options for the management of refractory epilepsy are still limited and AEDs, resective brain surgery and palliative procedures are possible choices among all alternatives. Failure of AEDs in controlling seizures after trials with two different medications in effective doses significantly reduces the chance of improving an outcome with another drug. Furthermore, despite the development of newer AEDs, there has not been an increase in efficacy or tolerability of conservative management. In these patients, brain surgery is still the most promising alternative and should be recommended when an identified epileptogenic focus can be resected without compromising eloquent areas. When the investigation is inconclusive, palliative procedures such as disconnecting surgeries or neurostimulation should be considered. One of the pillars of neurostimulation is VNS and, in approximately half of implanted patients, this can provide about 50% seizure reduction[4].

Since 1880, electrical VNS has been used to abort seizures or, at least, to decrease their frequency and duration. The neurologist James Corning was one of the predecessors of this procedure and his technique consisted of stimulating the vagus nerve transcutaneously, in conjunction with carotid compression. This method was initially proposed by Parry in 1792, with the intent of reducing cardiac output and, consequently, cerebral blood flow[5]. Apart from side effects, Corning was motivated by the outcomes, but his successors did not share his enthusiasm and the technique was subsequently abandoned. Nevertheless, in the 1950s, the interest in vagus nerve stimulation was resumed with animal studies, as well as its influence on electroencephalography (EEG). With promising outcomes in animals, a device for human use was designed and first implanted in the 1980s. In this preliminary study of four patients, two were seizure free, one had 40% improvement and one did not respond after implantation[6]. Additionally, encouraging results were also achieved in another series of five patients, published in the same year[7].

These were followed by double-blind, randomized studies, which were extremely relevant for the establishment of vagus nerve stimulation as an option for refractory epilepsy treatment and were also considered evidence for therapy approval by regulatory agencies in Europe and in the United States. Vagus nerve stimulation therapy was approved by the European community in 1994 and by the American community in 1997 and, nowadays, more than 70,000 patients have had implants for the treatment of epilepsy or depression[8].

The first controlled, multicenter study (EO3) examined 67 patients above 12 years of age with partial refractory epilepsy, who underwent VNS implantation and were randomized to high (20 to 50 Hz) versus low (1 to 2 Hz) frequency stimulation. After 14 weeks, the mean reduction in seizure frequency was

30.9% in the high frequency group against 11.3% in the low frequency group (p = 0.029), only the former being statistically significant when compared to the pre-operative status. Moreover, the responder rate (> 50% reduction in seizures) in the high frequency group was 38%[9]. After a year, a study of 114 patients older than 12 years, including the 67 cited previously, and following the same protocol, was published describing similar results[10]. Out of these 114 patients, 100 patients were followed in a non-blind study of high frequency VNS, with 20% reduction in seizure frequency in the first three months, 32% in the last 10 through 12 months and a response rate of 28% and 31%, respectively[11]. In another double-blind multicenter study (EO5), 196 VNS patients older than 12 years with partial refractory epilepsy were randomly assigned to high or low frequency stimulation and, after three months of follow-up, there was seizure reduction of 27.9% versus 15.2% in the high and low groups, respectively (p = 0.004). Better scores in global well-being evaluations were demonstrated (p < 0.001), but no statistical difference was achieved when comparing the responder rate[12]. After the blind phase, patients were invited to continue follow-up to analyze long-term outcomes (XE5 study). One hundred and ninety-five patients underwent high frequency stimulation (including the low frequency group) according to the same protocol of previous studies. After three months, there was 34% reduction in seizures and, after 12 months, 45% (p < 0,0001). Moreover, when shifted to high stimulation, the low stimulation group showed better seizure control, confirming the cumulative role of high frequency stimulation. Nevertheless, it is impossible to conclude that placebo effect (due to no control group) and variable parameters of stimulation, such as output current and pulse width, did not impact the results[13].

More recently, closed-loop stimulation, which has already been used for cerebral stimulation in epilepsy management, has been applied to vagus nerve stimulation. Ictal tachycardia has been observed in approximately 82% of patients with epilepsy, associated not only with generalized, but also focal, seizures. Although there is inter- and intra-individual variability, an increase of 30 bpm or 50% of basal cardiac rate is generally expected during a seizure[14]. Due to the adversities of continuous noninvasive monitoring, other methods of seizure detection were investigated and, in February of 2014, a new generator capable of detecting increases in cardiac frequency related to seizure initiation and trigger stimulation (responsive stimulation to ictal tachycardia) was approved in Europe. In one implanted patient, the system was very sensitive but not specific (92% and 13.5%, respectively). However, after three months of combined stimulation (cyclic and responsive), there was a reduction of seizure frequency and duration[15]. In 2015, the US - E 37 trial, a prospective and unblinded research for investigating VNS activated by ictal tachycardia, was also published. Short-term evaluation of 20 patients in the epilepsy monitoring unit after implantation showed that almost 35% of 89 seizures were treated by the responsive stimulation and 61% of them terminated. In the long term, the responder rate after 12 months was 50% and the adverse effects were similar to the previous VNS devices[16]. In another published prospective and multicenter study, short-term evaluation demonstrated that 40% of seizures were treated by closed-loop stimulation and 58% of them ended. However, the responder rate after 12 months was 30%, which could be explained by the parameters used during stimulation, with lower output currents than usual (1.250 mA)[17].

Anatomy

The vagus nerve, also known as 'X' cranial nerve, is relatively long and features sensory and motor innervation, as 80% of its fibers are afferent and 20% efferent[3]. It emerges from the posterolateral sulcus of the medulla in conjunction with the glossopharyngeal (IX) and accessory (XI) nerves, between the olive and cuneate/gracile fasciculi. Its efferent fibers, originated predominantly in the dorsal motor nucleus of the vagus and nucleus ambiguus, are responsible for the parasympathetic autonomic innervation of most of the thoracic and abdominal viscera along with motor innervation of the larynx and pharynx, respectively. Its afferent fibers convey visceral information to the solitary tract nucleus and, sequentially, to the locus coeruleus, hypothalamus, amygdala, thalamus and insular cortex. However, it is widely known that other brain regions, such as the spinal trigeminal nucleus, area postrema and reticular formation of the medulla can receive afferencies as well. Additionally, the vagus nerve is composed of three types of fibers: myelinated A fibers, predominately responsible for touch transmission; myelinated B fibers, responsible for visceral stimuli transmission; and unmyelinated C fibers, responsible for the transmission of pain. The vagus nerve is comprised mainly of C fibers and its conduction speed is rather slow (8.8 to 12.6 m/s)[18].

In the neck, the vagus nerve lies within the carotid sheath, deep between the carotid artery and the jugular vein. However, it is important to acknowledge anatomical differences between the right and left vagus nerves, primarily when planning for a surgical procedure. The preferential implantation of the electrode on the left is due to the innervation of the sinoatrial node by the right branches, which poses a greater risk of cardiac arrhythmias[3].

Mechanisms of action

The exact mechanism through which VNS exerts antiepileptic effects has not been completely elucidated yet. Although it has been demonstrated that type A fibers are the most excitable ones, followed by types B and C, respectively, it was once believed that all fibers should be stimulated to suppress seizures. Subsequently, scientists have found that C fibers are the ones responsible for the EEG desynchronization associated with epileptiform activity abolishment. Nevertheless, successive research has demonstrated that this effect was seen even after lesion of C fibers, suggesting that A and B fibers probably play a significant role[19].

Nowadays it is well established that VNS influences locus coeruleus and raphe nuclei to modulate cortical activity through alteration of noradrenergic and serotonergic projections[3]. The augmentation of locus coeruleus activity after electrical stimulation of the vagus nerve, demonstrated by an increase in c-fos, may provoke release of noradrenaline in the limbic circuit and activation of the dorsal raphe nucleus, which send diffuse serotonergic projections to the diencephalon and telencephalon. It is clear that VNS therapy induces variations in regional blood flow in different cortical areas including the thalamus, mesial temporal lobe, prefrontal cortex and limbic circuit, which is supported by neurofunctional imaging. Indeed, it has been postulated that modulation of some specific areas, such as the limbic circuit, could be related to better outcomes[20].

Surgical procedure

The surgical technique for VNS implantation was initially described by Reid[21] in 1990 and consists of coiling an electrode around the left vagus nerve and placing a generator in an infraclavicular pocket, which takes approximately one to two hours. The procedure starts with a horizontal cervical incision at the level of the cricothyroid membrane, from the midline to the medial border of the sternocleidomastoid muscle. After opening the platysma, it is often necessary to divide the omohyoid muscle to expose the carotid sheath. The vagus nerve is identified deep between the carotid artery and jugular vein and is later individualized to allow the placement of an electrode array of three spirals (a tethering coil, an anode and a cathode). The generator is implanted next, in a subfascial pocket in the left infraclavicular area, after tunneling the distal end of the electrode subcutaneously and securing the connections. The VNS is turned on 10 days after the procedure so one can differentiate adverse effects of stimulation from vagal dysfunction due to surgical manipulation. Besides being reversible and not causing neuroablation, the device can safely be explanted if needed[22], as in cases of lead breakage/malfunction or infection.

VNS settings

The VNS device allows programming of three fundamental parameters: output current, frequency and pulse width, in addition to on and off times (Figure 2). Although the settings currently used (Table 1) were derived initially from animal studies followed by human studies (EOS 1 to 5), they have not been clearly defined. Individual variations are considerably frequent due to the lack of conclusive randomized research that objectively compares different parameters. Ideal stimulation should target the delivery of the least amount of energy that would be sufficient to activate afferent fibers (responsible for the therapeutic effect) without compromising efferent fibers (responsible for side effects), and still augment battery life. The conduction velocity of efferent fibers, formed mainly by A fibers, are higher than the afferent ones, but the rheobase and chronaxie are the same or slightly different. In addition, the waveform and direction (anode placed proximally or distally) of stimulation apparently does not influence thresholds. Considering that A and B fibers are possibly the ones responsible for the VNS effects, understanding the complexity of their stimulation should enhance our knowledge on how to properly stimulate the vagus nerve. In fact, if these parameters could be monitored in an implanted patient, these data could be used as biomarkers to titrate stimulation and optimize therapy[23].

The output current varies from 0.0 to 3.5 mA, but initial programming is started at 0.25 to 0.5 mA. It is then gradually titrated monthly up to 1.75 to 2 mA, as the majority of vagal fibers will already be stimulated with currents around 1.5 to 2.25 mA[24]. It has been shown that the outcome in the first three months after implantation was very similar in groups that used output currents below and above 1 mA. Nevertheless, in unresponsive patients, the increase in current was associated with better seizure control, even though the current effect could be partially dependent on the stimulation period (increased response after longer stimulation periods)[25]. The threshold for vagal nerve stimulation in children is apparently higher than in adults, which could indicate the need for higher stimulation parameters (current or pulse width) to obtain similar effects[18].

In turn, frequency is set around 20 to 30 Hz, as values above 50 Hz can irreversibly damage the nerve[26] and 1 Hz stimulation is not as effective in controlling seizures[9]. In addition, pulse width is adjusted to 250-500 μs (Table 1).

The VNS is a cyclic stimulation with an 'on time' that usually lasts 30 seconds and an 'off time' of three to five minutes, although these parameters can be programmed according to the patient's response (Table 2). In a retrospective analysis of

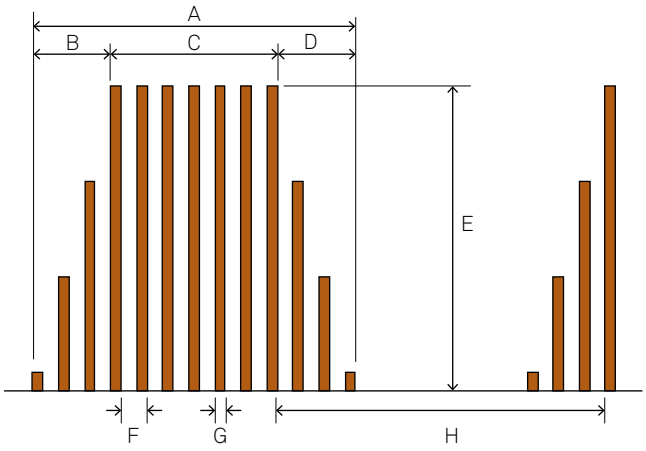

Figure 2. Diagram of VNS stimulation parameters.

Table 1. Suggestion of parameter adjustments on subsequent appointments.

Variable	1	2	3	4	5	6	7	8
Output current (mA)	0.25	0.5	0.75	1	1.25	1.5	1.5	1.5
Frequency (Hz)	20/30	20/30	20/30	20/30	20/30	20/30	20/30	20/30
Pulse width (μs)	250/500	250/500	250/500	250/500	250/500	250/500	250/500	250/500
ON time (sec)	30	30	30	30	30	30	30	30
OFF time (min)	5	5	5	5	5	5	3	1.8
Magnet current (mA)	0.5	0.75	1	1.25	1.5	1.75	1.75	1.75
Magnet ON time (sec)	60	60	60	60	60	60	60	60

Courtesy of Cyberonics, Inc.

stimulation settings in 154 patients (XE5 study), it was impossible to correlate a better outcome to modifications in current, frequency or pulse width after three and 12 months of follow-up. However, decreasing the 'off time' to 1.1 min or less in one group provided seizure reduction of 39%, as opposed to 21% in the group with baseline settings stimulation[27]. Although some researches advise fast stimulation (7 sec on and 30 sec off), no statistical superiority has been demonstrated yet[4]. Furthermore, increments in stimulation parameters will drain battery life and raise the need for generator replacement. Computational models have demonstrated that, even though a smaller number of fibers would be excited when pulse width is reduced from 500 to 250 μs, the required increase in output current, to keep the desired stimulus, consumes less energy[24]. Lower values of pulse width (250 μs) and frequency (20 Hz) may also be tried, to reduce adverse stimulation effects, according to the manufacturer's manual.

Besides the programmed stimulation provided automatically according to the predefined settings, the VNS system also allows an independent activation induced by the patient through a magnet, with the purpose of aborting an evolving seizure. This magnet-induced stimulation uses an output current of 0.25 mA higher than usual for twice the 'on' time. Boon et al.[28] was one of the pioneers in evaluating vagus nerve stimulation efficacy and noticed seizure interruption after magnet use in almost 60% of patients after three years of follow-up.

Seizure reduction rate

In 1999, a compilation of five clinical studies examining the long-term efficacy of VNS was published[29]. Four hundred and forty patients with partial (415 patients) or generalized (25 patients) epilepsy were followed for up to three years (396 for one year, 188 for two years, and 93 for three years). The response rate was 36.8% at one year, 43.2% at two years and 42.7% at three years, with 35% reduction in seizures in the first year, 44.3% after the second and 44.1% after the third year. Another review that included 1,104 implanted patients followed for two years[30], also corroborated the persistent effects of VNS. Subsequently, others have demonstrated VNS efficacy with increasing rates of responsive patients after four years (69%)[31] and five years (64%)[32], with mean seizure

Table 2. Duty cycles for various parameters.

OFF time (min)	Duty cycle (% ON time)				
	ON time (sec)				
	7	14	21	30	60
0.2	58*	69*	76*	81*	89*
0.3	44	56*	64*	71*	82*
0.5	30	41	49	57*	71*
0.8	20	29	36	44	59*
1.1	15	23	29	35	51*
1.8	10	15	19	25	38
3	6	9	12	16	27
5	4	6	8	10	18
10	2	3	4	5	10

*Not recommended; Courtesy of Cyberonics, INC.

reduction of 76% after 10 years ($p < 0,05$)[33]. Additionally, approximately 27% of implanted patients monitored for two years remained seizure free for more than one year[34].

In addition to focal epilepsy, VNS is also effective in treating other types of seizures, as initially shown by two pilot uncontrolled studies. According to Tecoma et al.[35], in a series of five patients with generalized epilepsy, two were seizure free and two were responders after six months. In Lennox-Gastaut syndrome there were promising results[36], with a 58% reduction in seizure frequency six months after implantation in a multicenter retrospective study of 50 patients[37]. SCN1A gene mutations might improve as well, as reported by Fulton et al.[38], who described a 75% rate of responders in 12 patients.

Similarly, VNS also played a relevant role in the management of refractory epilepsy in children, as observed in one of the major retrospective multicenter studies, which analyzed 347 children and found that 32.5% were responsive patients after six months, 37.6% after 12 months and 43.8% after 24 months[8]. When comparing patients younger and older than 12 years, no significant difference in efficacy or complication rate was demonstrated after five years of follow-up in 141 patients[39], although some reported increased infection rates in children[40].

Predictors of response have not been completely clarified, although some elements may have a prognostic value. In a cohort of 70 patients with partial or generalized epilepsy, there was an increase in response rate from 54% to 77% in patients younger than five years[41], which is in contrast to a multivariate analysis that demonstrated increased rates of seizure freedom in those who had an epilepsy onset above 12 years of age[42]. Besides age, unilateral EEG epileptiform activity was also correlated with a higher chance of seizure freedom[43]. In a series of 400 patients, the only predictive factor was focal change in the EEG ($p = 0,004$), apart from a tendency toward better results in focal epilepsy ($p = 0.09$)[44]. However, when analyzing different seizure types, generalized seizures were significantly associated with higher rates of seizure freedom during the first year, when compared to partial seizures[42].

Apart from these encouraging results, some could not confirm VNS efficacy. According to Hoppe et al., when compared to the best medical treatment, VNS associated with AEDs apparently did not benefit epileptic adults after one- or two-year follow-ups[45]. According to these authors, the efficacy of medical treatment is underestimated and VNS side effects may compromise quality of life, which justifies their results. However, it is essential to consider that VNS candidates often have catastrophic epilepsy, low functional capability and worse prognosis with progressive deterioration, regardless of therapy, which could compromise results.

Is of great importance to acknowledge that VNS effects are not immediate and seizure control improves gradually[46]. Moreover, the therapy may alter the course of the disease and reduce its progression as well.

Table 3 shows a summary of various studies evaluating high frequency VNS outcomes.

Quality of life

In addition to efficacy and seizure reduction, quality of life is another aspect that should be considered when evaluating VNS therapy, as psychosocial factors also contribute to score improvements. After assessing the quality of life of 17 VNS patients for one year, with a questionnaire regarding memory, physical and emotional well-being, depression and functional limitations (QOLIE-10), Ergene et al.[62] demonstrated that all scores improved significantly, regardless of seizure reduction ($p < 0.01$). Similar results were obtained in a cohort of 136 patients implanted with VNS, in which not only responsive but also unresponsive patients notably improved after three months of follow-up ($p < 0.0015$ and $p < 0.005$ respectively), with no statistical difference between the groups[46]. On the other hand, when analyzing quality of life in 19 children with Lennox-Gastaut syndrome, no statistical improvement in cognitive and behavioral scores could be detected after two years. Nevertheless, this should be carefully considered, as these children are usually severely impaired and outcomes could be adversely impacted[36].

Adverse effects

The most common side effects consist of hoarseness, dysphagia and coughing (recurrent laryngeal nerve stimulation or damage), discomfort or pain in the oropharynx (superior laryngeal nerve stimulation or damage) and dyspnea. These symptoms are generally induced by stimulation and may be very frequent during therapy initiation or after settings adjustments (approximately 60% of patients), but tend to decrease over time. Less frequent symptoms include bradycardia, asystole and facial paresis. These events are commonly managed by modifying stimulation parameters, such as reducing pulse width, without impairing seizure control. In 48 VNS patients, 14 experienced adverse effects using output currents between 1-3 mA, but improved completely after pulse width reduction from 500 to 250 or 130 μs, without an increase in seizure frequency[63]. Therefore, VNS therapy is well tolerated, with adverse effects predominantly induced by stimulation and generally reversible. Irreversible nerve damage, in turn, is usually rare[44].

Whereas studies report rates of 1% to 5% of hardware malfunction[4], these estimates are highly variable. Révész et al.[40] published a 3% incidence of lead breakage, noticed mainly by the increase of seizure frequency, as not all fractures are identified on imaging screening. Infection rates vary from 3% to 7% and, although generally treated with intravenous antibiotics and explantation of the device, some have described success managing these patients exclusively with oral antibiotics.

Cost-effectiveness

Although initial studies had demonstrated that VNS seemed to be an expensive therapy, long-term evaluations of emergency department visits and intensive care unit admission costs showed that these exceed VNS expenses during and after the implant. This could be justified by the increase in battery life after settings adjustments and the progressive rise in the number of responsive patients[64]. In a retrospective study of 536 adults who underwent VNS implantation, there was a reduction of 17% in emergency department admissions in the first year ($p = 0.03$) and 42% in the second year ($p = 0.01$).

Future Perspectives

Currently, one of the main goals in therapy improvement is to decrease patient risks, which can be achieved by increasing battery life and reducing the number of surgical procedures to replace the generator. According to the manufacturer's manual, setting decrements could augment device durability. A considerable percentage of VNS patients improve with low output currents, even after a belated course, as stimulation effects are not immediate. Moreover, decreasing frequency from 30 to 20 Hz and pulse width from 500 to 250 μs does not reduce the number of stimulated fibers and, consequently, does not interfere in treatment efficacy.

Another approach to improve patient care and increase battery life is the use of a rechargeable generator. This is

Table 3. Summary of evidence of high stimulation VNS outcome in the management of refractory epilepsy.

Authors and year	Class of evidence	No. of patients	Follow-up (mos)	> 50% reduction (%)	Mean or median % reduction (%)
Ben-Menachem et al., 1994[9]	I	67	3.5	38.7	30.9
George et al., 1994[47]	II	24	16–18	NR	52
Salinski et al., 1996[11]	II	100	12	18,40	32
Handforth et al., 1998[12]	I	94	3	NR	28
Ben-Menachem et al., 1999[48]	II	64	20 (3–64)	NR	45
Amar et al., 1999[49]	I	164	15	39	37 and 45*
Labar et al., 1999[50]	II	24	3	45.8	46
Vonck et al., 1999[34]	II	15	29 (12–48)	66.6	57.1
Parker et al., 1999[51]	III	15	12	26.6	17
Murphy et al., 1999[52]	III	51	18	NR	42
DeGiorgio et al., 2000[13]	II	195	12	35	45
Kawai et al., 2002[31]	III	13	56 (48–91)	69	63
Chavel et al., 2003[53]	III	23	24	61	54
Murphy et al., 2003[54]	III	96	32 (12–108)	45	NR
Uthman et al., 2004[55]	III	25	6–144	60	52**
Saneto et al., 2006[56]	III	43	18 (7–40)	51	51
De Herdt et al., 2007[57]	III	138	44 (12–120)	59	51
Ghaemi et al., 2010[43]	III	144	36 (24–71)	62	NR
Englot et al., 2011[30]	III	1104	24	56	62
Elliot et al., 2011[58]	III	65	124	NR	76.3 and 80*
Elliot et al., 2011[44]	III	400	59 (3–136)	64	55.8 and 59.2*
Ching et al., 2013[33]	III	100	6–144	51	49
Yu et al., 2014[59]	III	69	12	41	40
Orosz et al., 2014[8]	II	347	12	38	NR
Serdaroglu et al., 2016[60]	III	56	87	62.5	NR
Pakdaman et al., 2016[61]	II	44	60	11	67

NR: not reported; *mean and median; **evaluation at 144 mos.

already used in a few stimulation devices for the treatment of Parkinson's disease, dystonia and pain and allows stimulation to last for approximately nine years, compared to three years with non-rechargeable batteries. Although it may significantly reduce expenses, the rechargeable system has some disadvantages, mainly related to the need for routine charging of the battery. Possible permanent damaged in cases where it is not charged in an adequate time frame may occur as well. For epilepsy treatment with vagus nerve stimulation, a rechargeable system designated ADNS-300 has been tested in three patients. Its generator has a rechargeable battery that lasts for 12 years and its electrode consists of a spiral cuff, which contains two stimulation contacts (cathode and anode) and three recording contacts. Although output current parameters are empirically adjusted, it is possible to change settings in this design according to the recorded nerve activity, as was performed in two of the three patients[65].

The development of new electrode models can also contribute to therapy improvement. A new system used to treat cardiac insufficiency applies trapezoid instead of square waves to provide unidirectional stimulation through a cuff electrode in order to reduce side effects by decreasing external current loss. Preliminary analyses in epileptic patients have shown similar results to the VNS system, without side effects with stimulation of up to 2 mA[66].

Transcutaneous vagus nerve stimulation is another safe and well-tolerated alternative, developed to reduce surgical risks. In a randomized study comparing transcutaneous stimulation with placebo stimulation, there was a statistically significant reduction in seizures and improvement in quality of life after one year of follow-up[67].

The identification of response predictors would be of major importance in the improvement of therapy efficacy. Although some have linked EEG patterns, age of epilepsy onset and seizure types to better outcomes, as described previously, this association has not been reported consistently by all authors and no definite biomarker has been validated, decreasing the likelihood of properly selecting a patient population who would benefit the most. These could be justified by the heterogeneity of published data that makes comparison between series extremely difficult. Likewise, a thorough insight of the mechanism of action would promote an enhanced understanding of VNS parameters and possibly a larger success rate. Higher current intensities and longer pulse widths have been shown to increase firing of *locus*

coeruleus neurons, which would increase cortical norepinephrine levels and, consequently, reduce seizure frequency. However, it has been demonstrated that, in some situations, VNS response is maximal at moderate stimulation intensity, which could be explained by neurotransmitter depletion or inhibition mechanisms[68]. Therefore, future research to analyze therapy efficacy in homogeneous populations and to elucidate the areas involved in stimulation and their role in seizure control should be further encouraged.

Final Remarks

Vagus nerve stimulation is a safe therapy in the management of adult and pediatric patients with refractory epilepsy who are not candidates for resective surgery. There is currently level I evidence for its use in focal epilepsy and level II evidence for other seizure types. However, approximately one quarter of patients do not benefit from therapy and few achieve seizure freedom. Therefore, further research must be done to optimize parameters and improve efficacy.

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