Chapter 7

Vagus Nerve Stimulation Therapy for Epilepsy

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Additional information is available at the end of the chapter

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1. Introduction

The year 2013 marked the 25th year of clinical vagus nerve stimulation (VNS). This chapter will review the preclinical history, the clinical study history, and the long-term outcomes of VNS.

Epilepsy has been treated by many strange remedies over the centuries. In 1883, Corning [1] (Corning, 1883) proposed that vagus nerve stimulation could decrease heart rate and cerebral blood flow, thereby controlling seizures. This early attempt at vagus stimulation for seizure control quickly fell out of favor.

Bailey and Bremer [2] (Bailey & Bremer, 1938) demonstrated the direct effect of vagus stimulation on the central nervous system. They found that repetitive electrical stimulation of the central end of the vagus nerve of the cat results in increased amplitude and frequency of the spontaneous potentials of the orbital surface of the frontal lobes of the cerebral cortex. Inhibition of motor activity by activation of visceral vagal afferents was first reported by Schweitzer and Wright [3] (Schweitzer A, 1937) and later confirmed by Paintal [4] (Paintal, 1973). Dell and Olsen [5] (Dell P, 1951) reported that vagus stimulation affected slow wave activity in awake cats.

These papers and others led Zabara [6] (Zabara, 1992) to investigate vagus stimulation as a potential method to treat epilepsy. Zabara stimulated the cervical vagus nerve in a strychnine dog model of status epilepsy (N=20). He reported that vagus stimulation would interrupt the strychnine-induced seizure, and the amount of seizure interruption was proportional to the length of stimulation, approximately 4 times as long as the stimulation period. Vagal stimulation terminated seizures within 0.5-5 s. Transection of the vagus distal to the stimulating electrode did not alter the antiseizure effects of vagus stimulation. The optimal stimulus parameters were estimated to be approximately 20 volts (with electrode resistance 1-5 ohms), 20-30 Hz stimulation frequency and approximately 0.2 msec pulse duration.

In 1990 Lockard [7] (Lockard JS, 1990) used an alumnia gel chronic epilepsy model in monkeys. She induced chronic epilepsy by placing alumina gel on the cortex. Previous studies showed seizure rates remained stable for at least 6 months with this model. The instrumentation triggered a 40-second burst whenever it automatically detected a seizure. The stimulation device also provided a stimulation burst once every 3 hours. The stimulation frequency was changed in 2-week intervals from 83 HZ to 143 HZ and then to a random frequency ranging from 50-250 HZ. The stimulation amplitude was increased to tolerance or 5 mA. In 1 animal, investigators reduced seizure rate to near 0, then stopped stimulation and allowed seizures to return to baseline and restarted stimulation, thereby reducing seizure rate to near 0 once more. Seizure frequency was reduced to zero in a second animal, and stability of frequency was affected in the 2 remaining animals. The 3 stimulation patterns seemed to affect seizure rate equally, but the data were not statistically significant. Although Zabara [6] was able to interrupt seizures in the strychnine dog studies, no seizures were interrupted in the Lockard alumnia gel monkey study. The delay between detection and activation was tens of seconds and may have decreased the seizure interruption effect by VNS. Heart rate and blood pressure were unaffected, and stomach ulcers were not noted. The Woodburys [8] (Woodbury, 1991) theorized that stimulation during the seizure disrupts the seizure pathways in the brain, possibly "unlearning" the seizure mechanisms. They hypothesized that stimulation absent a seizure would not have an effect on reducing future seizures, but such a hypothesis has not been tested.

2. Clinical studies

2.1. Pilot studies

The VNS pilot study (E01) included 10 patients and was based on the Zabara [6], Lockard [7] and Woodbury [8] animal studies. Because technology for seizure detection did not exist at that time, the device was programmed to stimulate periodically, and patients received a magnet to self-activate the stimulation when they experienced an aura. As might be expected, most patients did not have auras and so they did not self-activate stimulation during the seizure. Investigators hoped this periodic pattern would occasionally occur during a seizure and eventually reduce the seizure frequency. Initial stimulation parameters were typically 250 μsec pulse width, 60 sec ON, 60 minutes OFF and 50 HZ, although a stimulation frequency of 143 HZ was used on the first patient. This pilot study was a single-blind study consisting of four seizure measurement periods: pre-implant baseline, stimulation period, sham stimulation period and stimulation period. The mean percent seizure reduction was 24.3% ($p<0.049$) after 4 months of treatment. [9] (Uthman BM W. B., 1993)

The 4-patient E02 pilot study was similar to E01, except pulse width was 500 μsec, ON time 30 sec, OFF time 10 minutes, and frequency 30 HZ. The mean percent reduction after the fourth treatment period was 39.9% ($p <0.074$).

The mean percent seizure reduction after 14 to 35 months was 46.6% for the combined E01 and E02 patients.[9] (Uthman BM, 1993) Two patients, one who previously had 10 to 100 seizures per day before stimulation, had been seizure-free for over 1 year [10]. (Penry JK, 1990)

The stimulation parameters used in the E01 study were quite different from those in current use, and the first study patient had a remarkable response to the high frequency and long OFF-time patterns.

2.2. E03 and E05 pivotal studies

In the 2 randomized, blinded, active-control trials (E03 and E05), patients were randomly assigned to either of 2 treatment groups: HIGH (believed to be therapeutic) or LOW (adjusted to patient perception but programmed to 1 HZ delivered once every 90 to 180 minutes; parameters believed to be less therapeutic). Patients enrolled in the study were seen every 4 weeks during the baseline period (weeks-12 to 0). Patients meeting eligibility were implanted with the pulse generator and lead are shown in Table 1. Output was adjusted to tolerance at each visit for both groups Table 1 provides descriptions of all study patients.

Description of Patients						
	Longitudinal			Parallel		
Study	**E01**	**E02**	**E04**	**E03**	**E05**	**Total**
No. of patients implanted	11	5	124	115	199	454
No. of patients stimulated	10	5	123	115	198	451
Age (range)	32 (20–58)	33 (18–42)	24 (3–63)	33 (13–57)	33 (13–60)	32 (3–63)
No. of females (%)	4 (36%)	2 (40%)	57 (46%)	43 (37%)	104 (52%)	210 (46%)
Years with epilepsy (range)	22 (13-32)	20 (5-36)	17 (0.8-48)	21 (4-47)	23 (2-52)	21 (0.8-52)
No. of AEDs (avg)	1.0	1.0	2.2	2.1	2.1	2.1
Median no. of seizures per day at baseline	0.6	0.42	0.65	0.70 high/ 0.85 low	0.58 high/ 0.51 low	-
All patients implanted in all VNS clinical studies, N=454 [13]						

Table 1. Description of Study Patients [13]

Two weeks after implantation, patients were randomized to the HIGH (frequency/duty cycle) or LOW (frequency/duty cycle) stimulation group, and the Pulse Generator was activated. Patients in the HIGH groups received a higher frequency, greater pulse width, and higher duty cycle of stimulation. The randomized treatment period that followed activation of the Pulse Generator lasted 14 weeks (the last 12 weeks of which were used in the efficacy analysis—the first 2 weeks were a treatment ramp-up period).

For the HIGH Group, a 30 Hz stimulation frequency was chosen based on the Woodbury rat studies [11] (Woodbury DM, 1990) and safety concerns by Agnew [12] (Agnew WF, 1990) that continuous stimulation at frequencies above 50 Hz might induce nerve damage, although the studies had shown that a 4-hour ON and 4-hour OFF at 50 HZ did not cause any damage. The E05 study used 20 Hz instead of 30 Hz. The 30 seconds ON and 5 minutes OFF was chosen as a compromise to extend battery life and achieve a 10% probability of stimulation during a seizure.

Results: The primary efficacy endpoint (percent reduction in seizure rate) was measured over 12 weeks as shown in Table 2. [13] (Cyberonics, 2013) Adverse events were assessed at each patient visit.

Principal Efficacy Results						
	Longitudinal			**Parallel**		
Study	**E01**	**E02**	**E04**	**E03**	**E05**	**Total**
No. of patients in efficacy analysis	10	5	116	114	196	441
Median reduction in seizures/day	32%*	48%	22%*	23% high*/ 6% low	23% high†/ 21% low†	-
Mean reduction in seizures/day	24%‡	40%	7%‡	24% high‡/ 6% low	28% high†/ 15% low†	-
Difference in mean (high/low)	-	-	-	17%§ (3%/31%)	13%‖ (2%/23%)	-
% with >50% response	30%	50%	29%	30% high/ 14% low	23% high/ 16% low	-
Principal Safety Results Through Long-term Follow Up						
Exposure (pt-yr)	45	20	245	456	135	901
SAEs¶ (high/low)	9%/ -	0%/ -	6%/ -	5%/0%	7%/9%	-
Discontinued (LOE/AE)#	0/1	0/0	2/3	0/2	1/3	3/9
No. of explants**	2	2	15	9	5	33
Deaths: SUDEP/total††	0/0	0/0	3/4	0/3	1/2	4/9

All patients in efficacy analyses in all VNS clinical studies, N=441 [13]

Within group broad analyses:

* P ≤ 0.05, by Wilcoxon sign rank.

† P < 0.0001, by anova.

‡ P ≤ 0.05, by Student's *t-test.*

Between group broad analyses:

§ P ≤ 0.02, by Wilcoxon rank sum; P ≤ 0.02, by Student's *t-test.*

‖ P < 0.04, by aligned ranks test; P < 0.02, by Student's *t-test*; P < 3.03, by anova.

Safety information:

¶ SAEs = serious adverse events.

Discontinuing for lack of efficacy (LOE)/adverse events (AE) at one year, excluding deaths.

** Number of explants through August 1996, excluding deaths.

†† All deaths occurred by the long-term follow-up closing date of August 1996.

Table 2. Principal Efficacy and Safety Results [13]

3. Regulatory approvals

More than 70 countries have approved vagus nerve stimulation (VNS) for refractory epilepsy. Table 3 lists several countries and regions. Caregivers should be familiar with the regulatory approval status in their own countries when reading this chapter. Reimbursement levels also vary by country.

The VNS therapy was also approved for depression, but is not being commercially marketed for this indication because of lack of reimbursement.

EPILEPSY	EU	USA	CANADA	CHINA	JAPAN
Year Approved	1994	1997	1998	2008	2010
Indicated age	All	12 and older	All	All	All
Indicated Seizure Type	All	Partial	All	All	All
DEPRESSION					
Year Approved	2001	2005	2001	N/A	N/A

Table 3. VNS Regulatory Approval Dates

3.1. Approved stimulation parameters

Parameter ranges currently available are provided in Table 4. The originally approved parameters included frequencies up to 143 HZ and output currents up to 12 mA, but these were later revised to those in Table 4 [13] (Cyberonics, 2013).

Stimulation Parameters	Available Parameter Settings
Output current	0-3.5 mA in 0.25-mA steps* ±0.25 ≤1 mA, ±10% > 1 mA
Signal frequency	1, 2, 5, 10, 15, 20, 25, 30 Hz, ±6%
Pulse width	130, 250, 500, 750, 1000 sec ±10%
Signal ON time	7, 14, 21, 30, 60 sec ±15% or + 7 sec, whichever is greater (±15% or ±7 sec in Magnet Mode)
Signal OFF time	0.2, 0.3, 0.5, 0.8, 1.1, 1.8, 3 min, and 5 to 180 min(5 to 60 in 5-min steps; 60 to 180 in 30-min steps), +4.4 / -8.4 sec
Magnet activation	Provided by magnet application (output current, pulse width, and signal ON time may be independently programmed for this purpose)

*The acute phase results include seizure frequencies of the E03 Study LOW stimulation group, which included one-half the E03 patients, N=57.

Patients were permitted to change their AEDs during these long-term follow-up studies, and these changes may have contributed to the change in seizure frequency.

Table 4. Stimulation Parameter Ranges [13]

4. American academy of neurology--vagus nerve stimulation guideline

A Report of the Guideline Development Subcommittee of the American Academy of Neurology (AAN RGDS), Evidence-based guideline update, Vagus nerve stimulation for the treatment of epilepsy, was approved by the AAN Board of Directors in June 2013 and published ahead of print in August 2013 [14] (Morris 2013). This proposed guideline is referenced in several places of this chapter and is based on Class III studies. Class III studies are typically controlled trials in which outcomes are independently assessed by objective outcome measures, whereas Class I and II studies are typically prospective randomized controlled blinded trials.

Some questions from AAN Evidence Based Guideline for Vagus Nerve Stimulation are discussed here.

4.1. Does efficacy improve over time?

The AAN RGDS [14] analyzed 2 Class III studies [15-16], (Morris GL III, 1999) (Kuba R, 2009), that outlined VNS efficacy after stimulation for more than 6 months up to 12 years. Both reports discussed mostly adult refractory seizures patients. With time, the number of responders (subjects who had ≥50% seizure decrease) increased slightly. No controls were made for change in medications, so independent assessment of the VNS effect was impossible. A study [15] of 440 adult clinical trial patients with partial epilepsy reported the >50% seizure frequency reduction grew from 36.8% of patients at 1 year, to 43.2% at 2 years, and 42.7% at 3 years. From baseline, median seizure reductions after 1 year were 35%, after 2 years were 44.3, and after 3 years were 44%. The Kuba study evaluated 90 patients with multiple seizure types and ages 13-64 years. The responder rate (≥50% reduction in seizures) increased from 41% after 1 year, to 53.2% of 87 patients after 2 years, and to 48.9% of 85 patients after 5 years. These reductions applied to partial and generalized seizures, with reduction rates of 70% among patients with generalized tonic-clonic seizures.

The AAN RGDS concluded, based on data from these 2 Class III studies, that VNS is possibly associated with an increase in the number of patients achieving a ≥50% reduction in seizures.

4.2. Efficacy at 10 and 12 years

In addition to the AAN RDGS publication, two papers reviewed long term efficacy. Elliott [17] (Elliott RE, 2011) reported on a group of 65 consecutive patients with 10.4 years average follow-up. At last follow-up, average seizure frequency decrease was 76.3%. Seizure reduction increased from 35.7% after 6 months, to 65.7% after 6 years and 75.5% after 10 years of VNS, a significant reduction from baseline at each measured interval ($P<0.0001$). Toward the end of the follow-up, the data indicated a trend of increased AED burden. Seizure frequency was significantly reduced from baseline at each of the recorded intervals ($P<0.001$). Data showed a trend toward increased AED burden in the latter years of the follow-up period.

In another study of 48 patients with intractable partial epilepsy, Uthman [18] (Uthman BM R.A., 2004) discussed a seizure reduction after 1 year of 26% with increases to 30% at 5 years and 52% at 12 years.

4.3. Experience with young children and with other types of seizures

4.3.1. Children

Among children with epilepsy, is using adjunctive VNS to reduce seizure frequency better than not using adjunctive VNS?

After reviewing 16 studies, the AAN RGDS [14] concluded VNS is possibly effective to achieve ≥50% seizure frequency reduction (responder rate) among children. A study of 481 children found a responder rate of 55% (95% confidence interval [CI] 51%–59%), but the data were considered heterogeneous. Of the 16 studies, 2 were not included owing to a lack of responder rate or else had too many (>20%) adults. Calculations placed the pooled seizure freedom rate at 7% (95% CI 5%–10%).

4.3.2. Lennox-Gastaut syndrome

In patients with LGS, is using adjunctive VNS to reduce seizures better than not using it?

The AAN RGDS [14] included 4 Class III studies about LGS patients that focused on younger patients. They stated that VNS is possibly effective among patients with LGS. A pooled analysis showed a 55% responder rate (113 patients; 95% CI 46%–64%).

4.3.3. Beyond AAN RGDS

In addition to the AAN RGDS publication, reviews of VNS for generalized seizures, secondarily generalized seizures, and Rett Syndrome have been published.

4.3.4. Generalized seizures

Cyberonics conducted an E04 study of 114 patients to provide additional data on vagus nerve stimulation for the treatment of medically resistant seizures, including generalized seizures and children older than 2 years.

Data were available for 25 patients with generalized seizures. Median decrease in seizure frequency during stimulation was 46.6% ($p<0.01$), 44% of patients had at least a 50% reduction in seizure frequency compared with baseline. Half of these patients were aged <18 years. However, no correlation was found between response and age. The treatment response in this group was largely driven by effects on generalized tonic clonic seizures [19]. (Salinsky, 1997)

Helmers [20] (Helmers SL D. M., 2011) reported grand mal status events decreased post-VNS compared with pre-VNS (adjusted IRR=0.79, $P<0.001$) in an analysis of 1655 patients in a multistate Medicaid database (January 1997-June 2009). The generalized seizure rate was reduced by about 67% after 3 years.

4.3.5. Secondary generalized seizures with Lennox Gastaut or Lennox Gastaut-like seizures

Cukiert [21] (Cukiert A, 2013) reported on 47 seizure types among 24 children. After VNS, seizure frequency reduction ≥50% was noted in 35 seizure types and 17 seizure types disappeared after VNS. Atypical absence, myoclonic, and generalized tonic-clonic seizures were significantly reduced by VNS; tonic and atonic seizures did not improve. Transient seizure frequency worsening was noted in 10 of the 24 children, at a mean output current of 3.1 mA.

4.3.6. Rett syndrome

Wilfong [22] (Wilfong AA, 2006) reported on a series of 7 patients with Rett syndrome. At 12 months, 6 of the 7 female patients had more than 50% reduction in seizures.

4.4. Does VNS improve mood in epilepsy patients?

Does VNS have a beneficial mood side effect in the treatment of epilepsy? Because VNS was approved for treatment-resistant depression by the FDA in 2005 and had already obtained a CE Mark for this indication in 2001, it could have beneficial effects on the mood of epilepsy patients.

AAN RGDS [14] cites 2 Class III studies showing significant improvements in standard patient-reported mood assessment scales in adult patients with epilepsy. Test results before implantation were compared with those afterward. One study [23] (Elger G, 2000)] evaluated 11 subjects 1, 3, and 6 months after implantation. Before VNS, 7 of the 11 patients met criteria for "sub depressive mood" by the Montgomery-Åsberg Depression Rating Scale, and group mean was within the subdepressive mood range; after implantation, group mean was in the nondepressed range. Likewise, 8 of the 11 met criteria for "mild negative symptoms" by the Scale for the Assessment of Negative Symptoms before VNS. Scale and subscale scores improved at the study's 3-month follow-up ($p < 0.05$). Mood improvements were sustained at the 6-month follow-up (9 of 11 subjects).

The second study [15] (Morris GL III, 1999) evaluated 20 subjects 3 months after VNS implantation. Results for change in subject-rated scales by t tests showed improvements in the clinician-administered Cornell Dysthymia Rating Scale ($p=0.001$) and the patient self-report Beck Depression Inventory (BDI) ($p=0.045$); results on the clinician-administered Hamilton Depression Index (investigator rated) also significantly improved. The group's mean BDI score pre–VNS treatment was 12.0 ("mild mood disturbance"); this decreased to 9.4 ("non depressed") after VNS. Further, BDI scores decreased relative to those for an epilepsy control group (no therapy) studied over the same period (by repeated measures analysis of variance, $p=0.07$). This benefit was not correlated with reduced seizure frequency or with stimulation frequency or intensity.

The AAN RGDS [14] concluded VNS is possibly effective for mood improvement among adults with epilepsy.

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5. Patient acceptance

Initiating VNS requires a surgical procedure to implant the generator and leads to begin the therapy. When the battery is depleted, surgery is required to replace the generator and replace the batteries. The leads are not usually disturbed during this procedure, but reattached to the new generator. Patient-perceived benefit has been hallmarked by the willingness of recipients to undergo surgical generator replacement across the history of the treatment. Morris [15] (Morris GL III, 1999) reported a 72% 3-year continuation rate among early users, and the November 11, 2013 Cyberonics Investor Conference Call placed it at 75% for the fully depleted Model 100 generators.

6. Battery life

The estimated battery life decreases as pulse width, frequency, output current, duty cycle, or lead impedance increases. For example, the Cyberonics Model 103 Manual [13] estimates battery life at more than 10 years for a stimulation frequency of 20 HZ, 1.5 mA output, 3 kohm impedance and 10% duty cycle for pulse widths ranging from 130 sec to 500 sec. Under the same conditions and a 50% duty cycle, the time to near end of battery life is 7.1 years, 6.2 years, and 3.7 years for pulse widths of 130 μsec, 250 μsec, and 500 μsec.

7. Cost effectiveness

The net cost of VNS determines medical cost reimbursement. Battery life drives cost savings after initial costs have been recouped.

Ben-Menachem [24-25] (Ben-Menachem E H. K., 2002) (Ben-Menachem E F. J., 2005) reports that implantation cost, when calculated over 8 years (battery life), is actually less than the cost of using a new AED over a similar time period. Real savings in hospital costs owing to seizures can also be expected. Average annual cost savings were approximately $3,000 per patient. This cost savings applied to all patients, whether or not they responded to VNS. These direct savings maintained over the battery life can equal or exceed the purchase price of the device.

In the Boon [26] (Boon P D. M., 2002) VNS group, mean seizure frequency decreased from 21 to 7 per month. Epilepsy-related direct medical costs (ERDMCs) in the VNS subgroup decreased from $4,826 to $2496 per year.

Bernstein [27] (Bernstein AL, 2007) compared average quarterly utilization rates of 138 patients for 12 months before device implantation with quarterly rates during 48 months of follow-up. Results during the 4th quarter of Year 4 revealed impressive decreases in utilization of all 4 measured aspects: a 91% decrease in outpatient visits, a 99% decrease in emergency department visits, a 67% decrease in hospital lengths of stay, and a 70% decrease in number of hospital admissions. Notably, no visits to the emergency department occurred during the final quarter of the study.

Helmers [20] (Helmers SL D. M., 2011) reported on 1655 patients in a pre-post analysis using multistate Medicaid data (January 1997-June 2009). After 1.5 years, she found VNS was associated with decreased resource utilization and epilepsy-related clinical events. The reduction in costs related to these hospital resources were equal to the initial costs related to the cost of purchasing and implanting the VNS System. Three years after the implant procedures the health care system had a net savings of $50,000 related to reduced hospitalizations and ER visits. Outpatient visits exceeded 50% of the total health care costs during the study. Table 5 gives the approximate net costs from Figure 2 in the Helmers paper. Using the trend line, net savings are projected for the remaining years of battery life.

Quarter	Cumulative Investment Return	
1	-$19,000	cost
2	-$17,000	cost
3	-$12,000	cost
4	-$7,000	cost
5	-$1,000	cost
6	+$4,000	savings
7	+$12,000	savings
8	+$19,000	savings
9	+$27,000	savings
10	+$34,000	savings
11	+$42,000	savings
12	+$50,000	savings
Projected Savings		
Year		
5	+$100,000	savings
7	+$150,000	savings
9	+$200,000	savings

Table 5. Cumulative adjusted Net Healthcare Costs from Baseline

These papers indicate marked savings to health care systems throughout the world, even though seizures are controlled in only 10-15% of patients. Primary cost saving drivers are reduced ER visits, reduced hospital admissions, and reduced hospital days.

8. Stimulation parameter selection

Selection of the output parameters consists of 2 steps. The first is full activation so that signals are sent to the brain. The second is selection of ON time, OFF time, and stimulation frequency to obtain optimum efficacy.

The vagus nerve consists of larger myelinated A and B fibers and smaller unmyelinated C fibers. The C fibers make up about 80% of the 100,000 fibers in the vagus nerve. Of the nerves going into the brain, about 80% are afferent. The ratios of A, B, and C are assumed to be the same for afferent and efferent fibers.

The approximate currents required to stimulate the A, B, and C fibers in the Woodbury paper are given in Table 6. [11]. The diameter of the rat vagus nerve is about 0.4 mm vs 2.0 mm diameter for the human vagus nerve.

Stimulation duration	A fiber	B fiber	C fiber
125 μseconds	10 μA	50 μA	325 μA
250 μseconds	5 μA	25 μA	200 μA
500 μseconds	5 μA	10 μA	125 μA

Table 6. Stimulation Current vs Pulse Duration in Rat Vagus Nerve Model [11].

Smith [28] (Smith CD, 2001) discussed right and left cervical vagus nerve measurements of a 4-canine study using the Cyberonics 300 Series Bipolar Vagus Nerve Electrodes (Figure 1). Smith reported the average A fiber chronaxie values were 75.4 ± 24.5 μs and were 82.3 ± 23.3 μs for B fibers. The A fiber rheobase values were 0.63 ± 0.18 mA and 0.66 ± 0.22 mA for B fibers. The A fiber propagation velocities were 59.0 ± 9.6 m/s and 43.4 ± 8.0 m/s for B fibers. An effective electrode area of 5 mm^2 yields current densities of ±13.0 mA/cm^2 and 12.9 mA/cm^2 for A and B fibers, respectively.

Understanding how stimulation parameters affect seizure control started with the Woodbury [11] (Woodbury DM, 1990) rat models of current, pulse width, stimulation frequency, and time delay necessary to inhibit a seizure. Rat vagus nerves are much smaller than human vagus nerves, rendering it difficult to translate the current used in the rat studies to human vagus nerve stimulation. The stimulation threshold, a function of current density, is determined by ratio of the cross sectional areas of the nerves, which is the ratio of the square of the diameters. (0.4 mm vs 2 mm). Therefore, equivalent stimulation current in humans should be approximately 25 times that of rat vagus stimulation. Activation of B fibers in the rats at 250 μsec was 25 μA, which would correspond to a 0.625 mA activation in humans using the 25 multiplication factor. This is very close to the range of that clinically being used. In 2012, Helmers [29] (Helmers SL, 2012) developed a computational model of the activation of the human vagus nerve. She tied the computational model to clinical experience in Table 7, which shows the approximate vagus nerve stimulation threshold strength–duration curve. Nonetheless, 25 years of clinical vagus nerve stimulation experience has yielded little direct measurement of vagus action potential.

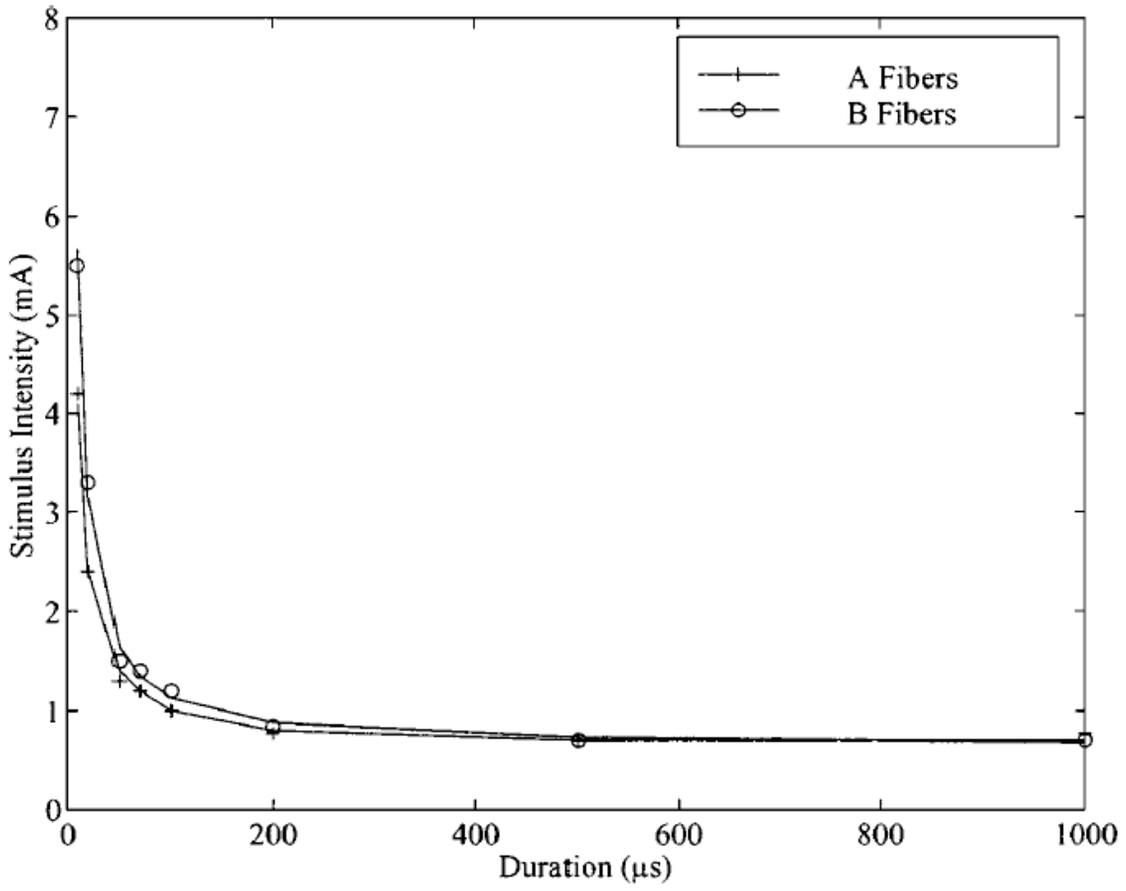

Figure 1. Chronixie and Propagation Velocity of Canine Vagus [28]

Pulse Width	6.3% range	57.5% range	36.2% range
130 usec	0.25-.1.0 mA	1.0-2.25 mA	2.25-3.5 mA
250 usec	0.25-0.75 mA	0.75-1.75 mA	1.75 -3.5 mA
500 usec	.0.25-0.6 mA	0.6-1.5 mA	1.5-3.5 mA

Table 7. Vagus Nerve Stimulation Threshold Strength–Duration Table [29]

The low number in the range is the 'minimum target' and represents the minimum output current pulse width needed to activate the nerve completely in the absence of tissue ingrowth. An increase in resistance because of tissue ingrowth may occur during the first several weeks after surgery. This increase may require additional stimulation per pulse for adequate recruitment of the vagal afferents. Very few patients (6.3%) responded with output current and pulse width falling below the 'minimum target' line. More than half of the responders (57.5%) had output current pulse width combinations above the 'minimum target' and below the high number or 'maximum target'; 36.2% of responders had output current pulse width combinations above the maximum target.

8.1. The stimulation S curve

Figure 2 shows that activation of the individual fibers in the vagus nerve follows the typical S curve as the current increases which assumes the activations threshold follows a normal distribution. For the A and B fibers, the 10% activation current (A) is believed to be about 0.25 mA and the 90% activation current (B) is believed to be about 1.5 mA. However, the curves have not been developed for individual patients and the curves are likely to vary among patients and may change over time for the individual patient.

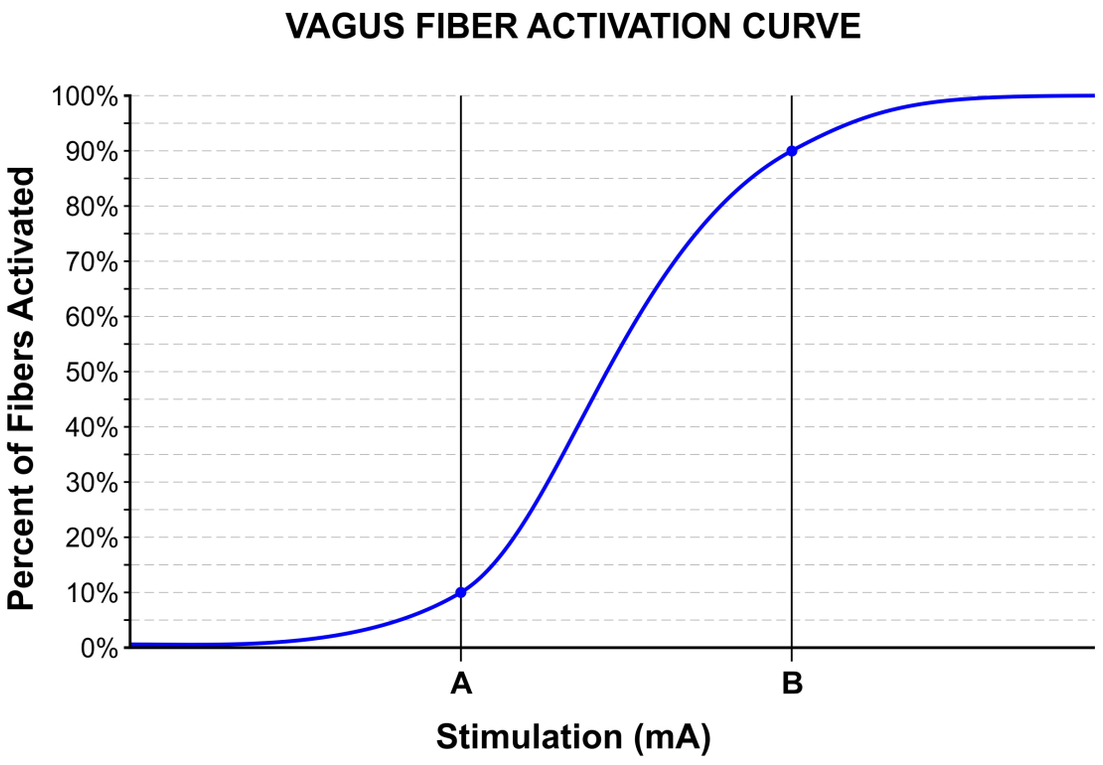

Figure 2. Fiber Activation Curve

8.2. Stimulation frequency

The typical stimulation frequency is 20 Hz, based on experience in the clinical studies and the Woodbury rat studies [11] (Woodbury DM, 1990). Woodbury reported that efficacy diminished rapidly with frequency reductions of 10 Hz and lower.

The E03 and E05 studies used 1 Hz for the placebo LOW group. Stimulation greater than 30 Hz may be equally or more effective, but battery life is shortened and patient discomfort may be increased.

8.3. Rapid stimulation or high duty cycle stimulation

The AAN RGDS [14] reviewed evidence on rapid stimulation cycles. Among patients receiving VNS, does rapid stimulation (usually 7 seconds “on” and 30 seconds “off”) improve seizure

frequency more often than standard stimulation settings (30 seconds "on" and 300 seconds "off")? In all the reviewed studies, beginning parameters were output current 0.25 mA, signal frequency 30 Hz, pulse width 250–500 ms, stimulation "on" time 30 seconds, and stimulation "off" time 300 seconds, and output current usually increased to 2–3 mA per tolerance. Schermann and collegues [30] (Scherrmann J, 2001) discussed rapid as opposed to standard stimulation settings, assessing results of 73 adult epilepsy patients with adjusted settings of standard (30 seconds "on" and 300 seconds "off", n=41) or rapid (7 seconds "on" and 30 seconds "off", n=32). After 2 years of follow-up, the standard stimulation group had greater overall seizure frequency reduction than the rapid stimulation group. In this article, the authors said a group receiving VNS at either standard or rapid stimulation did not demonstrate different response rates. For several patients, a changing to rapid stimulation several years after implantation improved outcome.

Concerning children, 2 Class III articles reported that rapid stimulation did not provide consistently better results than standard stimulation [31] (Alexopoulos AV, 2006) [32] (Shahwan A, 2009). According to the AAM RGDS, both studies lacked power to detect a difference between rapid stimulation when used either initially or after unsuccessful standard stimulation.

In contrast to the High Duty Cycle experience, very low duty cycles of 1 minute per hour have not been extensively studied, although success was observed in the E01 trial and such use would significantly extend battery life.

In summary, the physician has a range of parameter adjustments to optimize treatment for the individual patient.

9. Automatic seizure detection

Activation of VNS upon seizure detection was a long-time goal, but available technology limited such to self-activation by the patient or caregiver. A magnet, often worn on the patient's wrist, can be passed over the implanted generator to initiate stimulation. Morris [33] (Morris, 2003) conducted a retrospective analysis of magnet use during the E03 and E04 clinical trials of VNS. Magnet activation that aborted, decreased, terminated, or diminished a seizure was classified as an improvement; for purposes of evaluation, the patient was considered to have received a benefit. When patients in the E03 trial used magnets to activate stimulation, those in the active (HIGH) stimulation group reported more seizure improvement than those in the placebo (sham magnetic stimulation) group (P=0.0479, Fisher's test). In the E04 trial, 22% of the patients reported they were able to abort seizures and 31% reported the seizures were diminished.

Woodbury [11] (Woodbury DM, 1990) found that the length of the seizure was related to the length of delay between start of a PTZ-induced seizure in rats and start of stimulation. This rat study implied that stimulation should be initiated within the first 14 seconds of a PTZ-induced seizure. It seems intuitive that stimulation early in the seizure cycle would be most

effective and may explain why Lockard [7] was not successful in terminating seizures in the primate study.

Several papers have suggested the possibility of using heart rate changes to detect seizures, including Leutmezer [34] (Leutmezer F, 2003) and [35] (Schernthaner C, 1999). Luetmezer reported that 86.9% of all seizures were accompanied by ictal-onset tachycardia and 1.4% of seizures were accompanied by bradycardia. Patients with mesial temporal lobe epilepsy (TLE) were significantly more likely to have ictal HR increase than those with non-lesional TLE or extratemporal epilepsy. Ictal-onset tachycardia was also more likely with right hemispheric seizures. Interestingly, the increased ictal HR preceded the EEG onset by a statistically significant difference ($p=0.047$); average of 13.7 s among TLE patients and 8.2 s among extratemporal epilepsy patients.

Cyberonics developed the Aspire SR to provide seizure detection based on heart rate changes. Boon et al [36] (Boon P, 2013) had conducted the E36 prospective multicenter clinical study in Europe to evaluate seizure detection ability of the Aspire SR. Boon [36] had presented data on 31 patients at the 2013 American Epilepsy Meeting. The study met its primary endpoint of detecting more than 80% of seizures accompanied by ictal tachycardia and false rates were low. The detections occurred close to, and in some cases, before seizure onset. The AspireSR Generator can help patients for whom are not able to apply rapid and consistent hand-held magnet activation. For example, patients whom experience seizures while sleeping would benefit from this feature. The CE Mark for the AspireSR was issued in February 2014.

Neuropace has evaluated EEG detection for deep brain stimulation therapy. The study [37] (Morrell, 2011) found a statistically significant reduction in seizures with treatment group vs control group, but did not report an evaluation of detection sensitivity or false detection counts. [38] (Neuropace, 2013).

10. Vagus connections into neural networks

The vagus nerve comprises approximately 80% afferent fibers. These fibers enter the nucleus tractus solitaries and branch bi-laterally into both sides of the brain. For the most part, both the right and left vagus seem to have very similar projections into neural networks. Both project equally into the right and left sides of the brain, although they probably have many small differences.

Krahl [39] (Krahl SE C. K., 1998) reported data that indicate the LC is involved in the circuitry necessary for the anticonvulsant effects of VNS.

Naritoku [40] (Naritoku DK, 1995) began tracing the neural networks as did Cunningham [41] (Cunningham JT, 2008).

Naritoku [40] reported that specific nuclear fos immune labeling was induced by vagus nerve stimulation (VNS) in several forebrain structures, including the posterior cortical amygdaloid nucleus, cingulate, and retrosplenial cortex, ventromedial and arcuate hypothalamic nuclei.

The immune labeling was also apparent in the vagus nerve nuclei of the brainstem, in the A5 and locus ceruleus noradrenergic nuclei and in the cochlear nucleus. The sham-operated, unstimulated control animals had no fos immune labeling of these structures.

Cunningham studied the acute and chronic effects of VNS on brain structures using c-Fos and ΔFosB immune labeling. Acutely, VNS significantly increased c-Fos staining in the nucleus of the solitary tract, paraventricular nucleus of the hypothalamus, parabrachial nucleus, central bed nucleus of the stria terminalis, and locus coeruleus, but did not increase c-Fos staining in the cingulate cortex or dorsal raphe nucleus (DRN). VNS acute stimulation did not affect ΔFosB staining in any region. Chronically, VNS significantly increased both ΔFosB and c-Fos staining bilaterally in each region affected by acute VNS as well as in the cingulate cortex and DRN.

Cunningham [41] developed the neural network schematic in Figure 3, which was presented at several conferences.

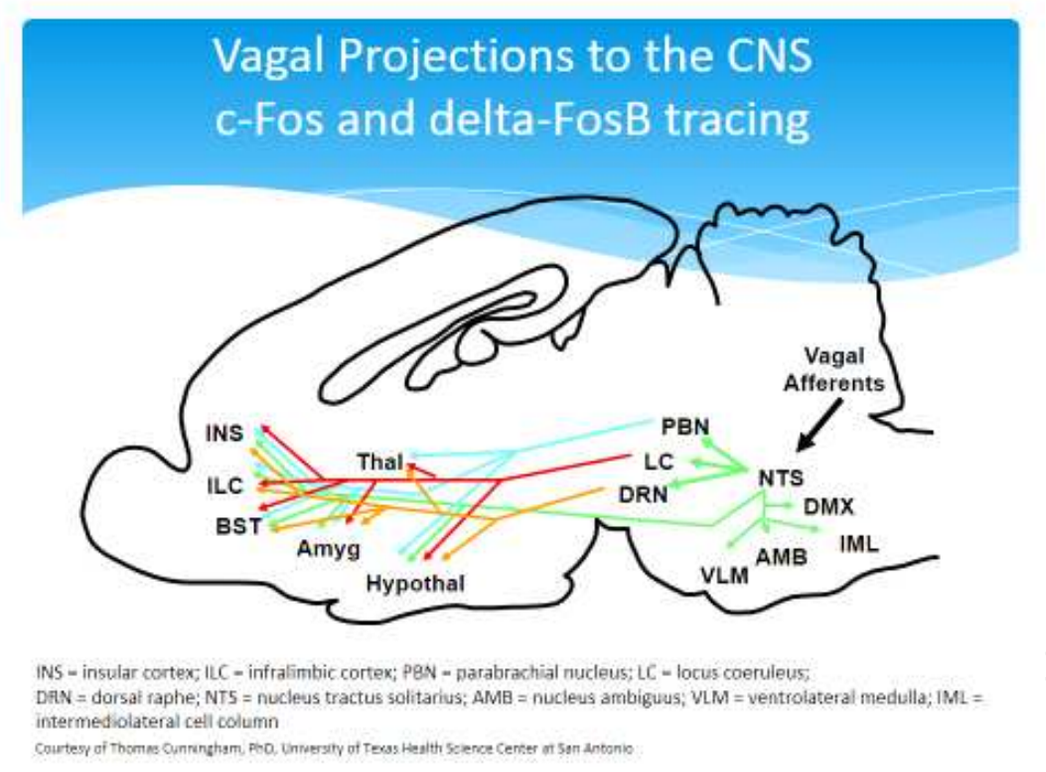

Figure 3. Vagal Projections to the Brain as Developed by Cunningham [41]

10.1. Left vs right vagus stimulation

In the clinical studies, the pulse generator was attached to the left vagus nerve for establishing safety and efficacy. Primate studies by Lockard [7] (Lockard JS, 1990) stimulated the right vagus nerve and noted no effect on heart rate nor gastric function. Several reports regarding right-sided stimulation among patients have not mentioned cardiac effects [42] (Navas M, 2010), [43] (Spuck S, 2008), [44] (Tubbs RS, 2007) (pig model), [45] (McGregor A, 2005) and [46]

(Krahl SE S. S., 2003) (rat model). Also, a positive clinical result from a pilot study of right vagus nerve stimulation for congestive heart failure has been published [47] (De Ferrari & Investigators, 2011). Although right-sided VNS may be safe, it should be used cautiously as its safety has not been established in clinical studies.

Would stimulation of both the right and left vagus nerve have an additive effect that might improve efficacy? This approach has not been studied in animal epilepsy models.

11. External vagus stimulation

The concept of using external stimulation has appeal because VNS requires surgical implantation, and not all patients respond. Two external vagus stimulation devices and 1 trigeminal nerve stimulator are being investigated in clinical studies. Although these devices have CE Mark approval for 1 or more indications, none have FDA approval as of February 2014.

Stefan [48] (Stefan H, 2012) described the Cerbomed NEMOS device used in a pilot study among 10 patients. Electrical stimulation was applied transcutaneously to the auricular branch of the vagus nerve (ABVN) of the left ear. Three patients left the study. Of the remaining 7 patients, 5 experienced an overall seizure reduction after 9 months of t-VNS.

DeGeorgio [49] (DeGiorgio CM, 2013) reported a 50-patient double-blind trial of the Monarch™ eTNS Trigeminal nerve stimulation device by NeuroSigma, and Pack [50] (Pack AM, 2013) commented on the study. No significant differences were found between the active group and control group in any of the 3 predefined primary end points, but a significant within-group difference improvement was seen in the responder rate over the 18-week treatment period. The responder rate was 17.8% at 6 weeks, and it increased to 40.5% at 18 weeks, providing a significant within-group improvement (p=0.01). Pack [50] commented that it is unclear how the responder rates at the serial observation periods were derived and concluded that although interesting, these data do not support the effectiveness of eTNS for the treatment of refractory partial seizures.

Electrocore Medical makes the gammaCore battery-powered device that is held against the neck and provides a single 180-second burst of vagus nerve stimulation. A number of presentations and publications of pilot studies have reported encouraging results for migraine, cluster headaches, asthma, and bronchial COPD. Electrocore Medical has a CE Mark for epilepsy, but no epilepsy studies have been reported as of February 2014.

12. Deep brain stimulation

Deep brain stimulation is attractive because it stimulates the specific part of the brain associated with the seizure. Medtronic and Neuropace have conducted clinical trials with devices that provide deep brain stimulation. Both have CE Mark approval and Neuropace received FDA approval in November 2013.

Fisher [51] (Fisher R, 2010) reported on the 110-patient double-blind trial employing the Medtronic dual-channel Model 7428 Kinetra Neurostimulator. During the final blinded month, seizure reduction was 29% greater among the stimulated group than the controls, (GEE) model (p=0.002). At 2 years, median percent reduction in seizure frequency was 56%; 54% showed seizure reduction of at least 50%, and 14 were seizure-free 6 months or more.

The Neuropace RNS® System detects seizures from the EEG and then initiates stimulation. Morrell [37] (Morrell, 2011) reported on the 191-patient double-blind study of the Neuropace System. Although seizures were significantly reduced during the blinded period for both the treatment and sham groups, the treatment group seizures were more significantly reduced (-37.9%, n=97) compared with the sham group (-17.3%, n=94; *p*=0.012). There was no difference in adverse events between groups during the blinded period. The treatment group sustained seizure reduction. The FDA approved the Neuropace RNS® System in November 2013.

13. Conclusion

During its first 25 years, meaningful advances have been made in VNS for epilepsy. More than 70,000 patients have been treated and more than 100,000 devices have been implanted, which includes battery replacements. Long-term clinical experience shows that efficacy continues to improve, which is different from many pharmaceutical therapies. The therapy is highly cost effective, resulting in considerable long-term savings even though most patents do not become totally seizure free. Much is still to be learned about VNS. Advances continue regarding methods of seizure detection and activation therapy. Various methods of external stimulation as well as deep brain stimulation are being developed and evaluated.

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