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Vagus nerve stimulation therapy in depression and epilepsy: therapeutic parameter settings

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Vagus nerve stimulation (VNS) therapy is an effective adjunctive treatment for chronic or recurrent treatment-resistant depression in adults, and for pharmacoresistant epilepsy in adults and adolescents. VNS therapy is administered through an implanted pulse generator that delivers programmed electrical pulses through an implanted lead to the left vagus nerve. Programmable pulse parameters include output current, frequency, pulse width, and ON/OFF times. Within a range of typical values, individual patients respond best to different combinations of parameter settings. The physician must identify the optimum settings for each patient while balancing the goals of maximizing efficacy, minimizing side effects, and preserving battery life. Output current is gradually increased from 0.25 mA to the maximum tolerable level (maximum, 3.5 mA); typical therapeutic settings range from 1.0 to 1.5 mA. Greater output current is associated with increased side effects, including voice alteration, cough, a feeling of throat tightening, and dyspnea. Frequency is typically programmed at 20 Hz in depression and 30 Hz in epilepsy. Pulse width is typically 250 or 500 μs. The recommended initial ON time is 30 s, followed by 5 min OFF; OFF time > ON time is recommended. As with pharmacotherapy, VNS therapy must be adjusted in a gradual, systematic fashion to individualize therapy for each patient.

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Introduction

Vagus nerve stimulation (VNS) therapy is an effective adjunctive treatment in adult patients with chronic or recurrent treatment-resistant depression (TRD) and for pharmacoresistant epilepsy in adults and adolescents (1, 2). VNS therapy is administered through a small pulse generator implanted subcutaneously in the left thoracic area, which delivers programmed electrical pulses through an implanted lead to the left vagus nerve in the neck. VNS therapy has been administered to more than 40,000 patients worldwide, representing more than 100,000 patient-years of treatment experience in more than 24 countries (3). VNS therapy was approved in the US for epilepsy in 1997 and for depression in July 2005 (4). In spite of the extensive use of VNS therapy, its mechanisms of action in epilepsy and depression are not fully understood and are beyond the scope of this article. However, three aspects of the therapeutic mechanisms of VNS therapy that affect the setting of therapeutic parameters are discussed here: the role of C-fibers, the functions of the locus coeruleus in epilepsy and depression, and changes in the effect of VNS therapy over time in depression.

It was initially thought that the benefits of VNS therapy in epilepsy were mediated by unmyelinated C-fibers (5). This theory was discounted after Krahl et al. demonstrated in animals that activation of C-fibers was not necessary for VNS antiseizure effect (6) and a human study showed that the levels of stimulation used to treat epilepsy are below the threshold necessary to activate C-fibers (7). In animal studies, Krahl et al. (6) found that activation of the locus coeruleus by VNS therapy is a critical component of the

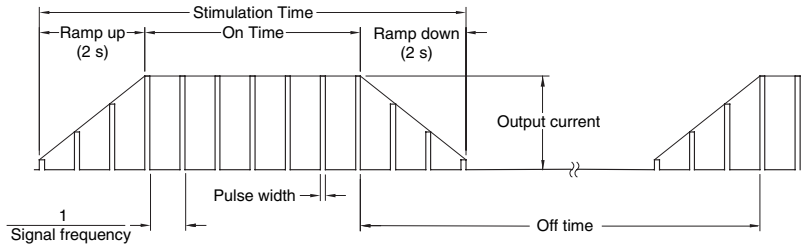

Figure 1. Pulse generator output parameters.

anticonvulsant activity of VNS in epilepsy. In addition, they observed that VNS induces an increased release of norepinephrine, which may mediate the antiseizure effects of VNS therapy in epilepsy and play a role in the action of VNS therapy in depression (6, 8). George et al. (5) observed VNS-induced changes in the limbic and paralimbic regions that modulate mood and that effects of VNS therapy observed after long-term therapy are different from the immediate effects. Immediately after the start of therapy, magnetic resonance imaging observations detected increased blood flow in the orbitofrontal cortex, cerebellum, insula, and medial and dorsolateral prefrontal cortex. After 3 months, imaging studies showed further increases of blood flow in areas involved in mood and anxiety regulation, including the orbitofrontal, medial, prefrontal, insula, and cingulate cortex, and showed no areas with decreased blood flow (5).

Parameters of VNS therapy

Programmable parameters of the pulse generator used in VNS therapy are output current, frequency, pulse width, and ON and OFF times (Fig. 1). Parameters can be varied for each patient to maximize tolerability and adjusted according to the efficacy results (9–11). This article discusses each VNS therapy parameter and describes the interactions among them, summarizing evidence from key clinical studies and our own experience. Our objective is to help physicians develop a strategy for identifying the optimum settings for each patient while balancing the goals of maximizing efficacy, minimizing treatment-emergent side effects, and preserving battery life.

Methods

Clinical studies in depression selected for this review include an open-label pilot study of 60 patients (D01) (9, 12) and a controlled pivotal study of 233 patients in acute and naturalistic long-term phases (D02) (1, 13). We also analyzed a controlled multicenter study (E05) of acute and long-term VNS therapy in 194 patients with intractable epilepsy (2, 10, 14) (Table 1). In the E05 study, the acute phase (initial controlled study period) was followed by a naturalistic long-term follow-up phase during which patients who had received sham treatment could receive active VNS therapy (13). Follow-up during this phase was 9 months for patients who had been in the active treatment group and 12 months for those in the original sham treatment group, so that all patients had a total of 12 months of VNS therapy. Parameter settings could be adjusted at the physician's discretion during this phase of treatment.

Also included were prospective (7, 11, 15, 16) and retrospective studies (17, 18) of the effects of parameter setting changes in patients with epilepsy. These studies were selected for inclusion because the published journal reports contain specific data about parameter settings used; other studies of clinical trials of VNS therapy were excluded because they did not describe parameter values in sufficient detail for our analysis.

While some of the prospective studies (7, 11, 15, 16) were designed specifically to identify optimal parameter settings, many were not, and the responses of individual patients to particular parameter settings were not captured during the studies. Because of interactions among stimulation parameters, it is difficult to identify effects of individual parameter changes. The Labar study (17) has the limitations common to post-marketing registry studies: participation was voluntary, potentially biasing patient selection. In this study, several factors make it difficult to compare patients in the registry: diagnostic and classification criteria were not standardized, no control group was evaluated, and patients were receiving a variety of treatments.

Output current

Output current is the amplitude of the current delivered in a single pulse of stimulation, measured

Table 1 Stimulation parameters in clinical studies

Indication	Study	Time of parameter recording	Parameter and value					
			Output current	Frequency	Pulse width	ON time	OFF time	Notes
Depression	Pilot (D01) (9)	8 weeks	Median: 0.75 mA Range: 0.25–3.0 mA	20 Hz ($n = 49$) 30 Hz ($n = 11$)	500 μs ($n = 57$) 250 μs ($n = 3$)	30 s ($n = 60$)	5 min ($n = 56$) 3 min ($n = 4$)	No adjustment of parameters for efficacy
	Pivotal (D02) (13)	12 months	Median: 1 mA Range: 0–2.25 mA	Median: 20 Hz Range: 2–30 Hz	Median: 500 μs Range: 130–750 μs	Median: 30 s Range: 7–60 s	Median: 5 min Range: 0.3–180 min	Most patients stayed at 3-month settings except for output current, which was increased
Epilepsy	Controlled multicenter E05 (14)	12 months	Mean: 1.7 ± 0.8 mA	Mean: 28.6 ± 4.0 Hz	Mean: 612 ± 153 μs	Mean: 30.9 ± 13.7 s	Mean: 3.7 ± 2.3 min	Nonsignificant correlation between increased output current and reduction in seizures in overall population, but longer duty cycles benefited some patients
	Parameter study (11)	3 months	Mean (SD) (three groups): 0.87 (0.39) mA 0.80 (0.36) mA 0.93 (0.54) mA	3 groups[1]: 20 Hz 20 Hz 30 Hz	3 groups[1]: 500 μs 250 μs 500 μs	3 groups[1]: 7 s 30 s 30 s	3 groups[1]: 18 s 30 s 3 min	All three duty cycles equally effective as initial therapy
	Registry study (17)	12 months	0.25–1.0 mA ($n = 76$) 1.25–2.0 mA ($n = 147$) ≥ 2.25 mA ($n = 46$)				≥ 5.0 ($n = 121$) 3.0 ($n = 56$) 1.8 ($n = 17$) ≤ 1.1 ($n = 75$)	Changes in parameter settings from month 3 to month 12 had no significant effect on efficacy

SD, standard deviation.

[1]Changes in frequency, pulse width, or ON/OFF times not permitted in the study.

in milliamperes (mA). The output current is one component of the charge delivered per pulse, which is expressed in microCoulombs (μC) and is calculated by multiplying the output current in milliamperes (mA) times the pulse width in microseconds (μs). The output current of the pulse generator ranges from 0 (device off) to 3.5 mA in 0.25 mA steps (Table 3).

Output current is set at 0.25 mA at the start of VNS therapy, and increased in 0.25–0.5 mA steps every 2–4 weeks as patient tolerability permits. The onset of benefit may not be immediate. For most patients, onset is generally slow and response to therapy improves with time. At the beginning of treatment with VNS therapy, patient tolerability is the primary consideration; tolerability to increased output current may improve over time.

Output current in clinical studies (Table 1)

Depression

Output current settings for patients with depression were evaluated in the D01 study (9). After a 2-week stimulation adjustment period, the median output current was 0.75 mA during an 8-week fixed stimulation period (mean 0.96 ± 0.54; range 0.25–3.0 mA) (12). A lower output current was associated with a better treatment response ($P = 0.07$) during the acute phase of the pilot study (9, 12). The authors urged caution in interpreting these findings, because parameters were adjusted only during the initial 2 weeks of VNS therapy, and no attempt was made to adjust parameters to optimize efficacy during the remaining 10 weeks of the acute phase of the study. In addition, this observation may reflect the difference between responders and nonresponders to therapy. Improvement in depression, when it occurred, typically took longer than the 2 weeks during which the protocol permitted the adjustment of parameters.

In the D02 study (1) of VNS therapy in depression, participants started therapy with an output current of 0.25 mA, which could be adjusted in 0.25 mA increments over the initial 2 weeks of the study. The median output current value at the last recorded visit of the acute phase (approximately 10 weeks after the start of VNS therapy) was 0.75 mA (mean 0.67 ± 0.33; range 0–1.5 mA). The rate of response to therapy [≥50% reduction in scores on the Hamilton Rating Scale for Depression (HAM-D)] after 10 weeks in this study was 15%, a negative result for the primary endpoint (1); the response rate increased to 27.2% after 12 months (13). An exploratory analysis by the investigators found no relationship between output current values and percent of change in HAM-D scores (1). The median output current setting after 12 months was 1.0 mA (range 0–2.25 mA). Our preliminary observation during the trial was that a higher charge delivered per pulse may have been associated with a better response.

The median output currents and ranges used in these clinical studies of TRD were 0.75 mA (range 0–1.5 mA) in the acute phase of the pivotal trial (12) and 1.0 mA (range 0–2.25 mA) after 12 months in the naturalistic follow-up phase of the pivotal trial (1).

Epilepsy

In the E05 study, the average current setting for the active treatment group was 1.3 mA after 3 months (2) and 1.7 ± 0.8 mA after 12 months of VNS therapy (14). At 12 months, there was a weak, nonsignificant correlation between increased output current and a reduction in seizures. In a 2005 study of changes in parameters for VNS therapy for 61 patients (11), the mean output current ranged from 0.87 to 0.93 mA (standard deviation 0.36–0.54 mA) in three treatment groups. Differences in output current had no significant effect on the 50% response rate for patients in that study.

In contrast, results of a registry study (17) suggest that high output currents (≥ 2.25 mA) may be less effective than lower currents. The study retrospectively evaluated the effects of output currents on seizure rates of 269 patients who had not changed their antiepileptic medication over a 1-year period. Output currents were classified as low (0.25–1.0 mA), medium (1.25–2.0 mA), or high (≥ 2.25 mA). Patients receiving a high output current experienced less reduction in seizure rate (median 38%) than those with low (64%) or medium (61%) output currents ($P = 0.0197$). Explanations offered for these results include the possibility that high currents increase the seizure rate in some patients. It is also possible that physicians increased the output currents in patients who did not respond initially to lower settings, and that patients who did not respond to lower current settings would have been unlikely to respond to VNS therapy at *any* parameter settings.

Safety and tolerability during use

Potential side effects of VNS therapy increase with output current, and include voice alteration or hoarseness, cough, a feeling of throat tightening, and dyspnea. In an evaluation of 440 patients over 3 years of VNS therapy, Morris et al. (18) observed

that these side effects tend to diminish with time. Most patients become accustomed to successively higher output current levels if adjustments are made in 0.25–0.5 mA increments over time, with 2–4 weeks between each increase. In three clinical studies (12, 14, 18), 24-h Holter monitor results for patients undergoing VNS therapy did not reveal any clinically relevant cardiac effects at recommended settings.

Safety and tolerability during implantation

Tatum et al. (19) described four cases of transient bradycardia followed by asystole during implant procedures, which occurred during intra-operative lead testing. In another case (20), transient asystole occurred when a test of the VNS system lead was attempted with an output current of 1.0 mA. Ben-Menachem noted that all reported cases of asystole occurred in the operating room (21). This rare effect of stimulation seems to be related to the consequence of *de novo* stimulation of a previously untreated nerve at a relatively high current.

The Cyberonics Physician's Manual (22) notes that some infrequent incidents of bradycardia with or without asystole have occurred during the intraoperative lead test. The manual states that clinicians should be prepared to follow procedures consistent with Advanced Cardiac Life Support (ACLS) guidelines if, during the lead test or when stimulation is initiated, a patient experiences severe bradycardia (heart rate < 40 beats/min) or a clinically significant change in heart rate occurs.

Frequency

Frequency is the repetition rate of pulses, measured in the number of pulses per second (Hz). The frequency of the pulse generator ranges from 1 to 30 Hz (Fig. 1, Table 3). In preclinical studies, the optimum frequency was found to be between 20 and 30 Hz (23).

Frequency in clinical studies (Table 1)

Depression – In the D01 study (12), 11 patients were treated at 30 Hz and 49 patients were treated at 20 Hz; the protocol was amended to change the specified frequency from 30 to 20 Hz (9, 24). This change was based on data from animal studies by Woodbury and Woodbury suggesting that 20 Hz was sufficient for stimulation (24). In the D02 acute study, the median value at the last recorded visit was 20 Hz, with a range from 10 to 20 Hz (1). At 12 months, the median stimulation frequency was 20 Hz and ranged up to 30 Hz (13).

Epilepsy – In the E05 study, patients were randomly assigned to receive either low-stimulation VNS therapy (active control) at a frequency of 1 Hz, or high-stimulation active VNS therapy at a frequency of 30 Hz (2). Frequency settings were changed in both groups over the course of the trial as physicians titrated settings. The mean pulse generator frequency for the high-stimulation group was 29.8 ± 1.4 Hz at 1 month and 28.6 ± 4.0 Hz at 12 months (14). Both the high-stimulation and low-stimulation groups experienced significant decreases from baseline to 12 months in the number of seizures. (In this study, patients originally assigned to the 1 Hz control group were crossed over to active treatment after 3 months.) In the 2005 study of parameter settings in epilepsy (11), patients were assigned to fixed frequencies of either 20 Hz (two groups) or 30 Hz (three groups). Frequency differences were primarily employed to diminish side effects, and were not believed to affect treatment efficacy. In clinical practice, many patients with epilepsy have their pulse generators programmed to 20 Hz.

Koo et al. (15) evaluated VNS therapy parameters in 21 patients with epilepsy, aged 4–31 years (mean 14.14 ± 6.98 years). Children in the study had a slower conduction velocity than adults, suggesting that the vagus nerve is not mature in children. The investigators determined that for children, a lower stimulation frequency than is used for adults may achieve a therapeutic effect; they recommended 20 Hz or lower (15).

Based on clinical study data, an initial frequency of 20 Hz should be used for patients with depression (1, 9, 12, 13) and 30 Hz for patients with epilepsy (2, 11). Frequencies of 5 Hz or lower should be avoided because they are not effective and deplete the battery (22, 25). The device manufacturer states that, for patients with obstructive sleep apnea, lowering the stimulus frequency may prevent exacerbation of apnea (25).

Pulse width

Pulse width is the duration of a single pulse of stimulation (Fig. 1) and is measured in microseconds (μs). Pulse width multiplied by the output current yields the stimulation output, measured as the charge delivered per pulse. The range of pulse width is 130–1000 μs (Table 3); pulses are unidirectional (23). The pulse width setting affects the level of output current required to stimulate the vagus nerve, and higher output currents may be needed for shorter pulse widths

(23). This phenomenon appears to be age dependent; younger patients may require higher output current or longer pulse widths for effective stimulation (15).

Pulse width in clinical studies (Table 1)

Depression – In the D01 study (9), pulse width settings were 500 μs for 57 patients and 250 μs for three patients. These patients had various combinations of frequency and ON and OFF time settings. In the D02 study, the median pulse width values at 3 and 12 months were 500 μs, with a range from 130 to 750 μs (13).

Epilepsy – In the E05 study (2), all patients were treated at a 500 μs pulse width during the 3-month double-blind treatment phase. During the 12-month follow-on phase, the mean pulse width was 612 ± 153 μs at 12 months (14). In the 2005 study of stimulation parameters (11), patients were randomly assigned to receive VNS therapy with fixed pulse width settings of either 250 or 500 μs. The mean output current for the group assigned to a pulse width of 250 μs was slightly lower (0.80) than the mean output current for the 500-μs group (0.87 or 0.93). Pulse width differences among the treatment groups at the end of the study were slight, the authors said, and were employed to diminish side effects (11).

Safety/tolerability – Liporace et al. (16) reported that reductions in pulse width from 500 to 250 μs increased the tolerability of VNS therapy in epilepsy without affecting seizure control, confirming findings reported previously by Labiner et al. (7). In a clinical study described by Liporace et al. (16), 14 of 48 patients (29%) receiving stimulation at 500 μs reported pain in the neck, throat, or jaw and teeth. One of those patients also reported coughing, and another reported muscular contractions in the neck when stimulation was activated. Reducing the pulse width to 250 μs resulted in immediate and complete resolution of pain for 10 patients; reduction of the pulse width to 130 μs was required for four patients. For all 14 patients in whom the pulse width was reduced, pain relief was complete even when mean output current was increased from 2.0 to 2.5 mA at the lower pulse width setting. Two patients also noted a smaller degree of voice alteration at the lower pulse width (16).

In the study by Koo et al. (15), the current required for effective stimulation increased as pulse width decreased; this effect was most prominent with pulse widths below 100 μs, especially in children younger than 12 years. The authors note that a pulse width setting below 130 μs (the lowest programmable value of the currently available pulse generator) should not be used because of the high current values required to activate the nerve (15).

Duty cycle

Stimulation is administered intermittently, with alternating periods of programmed signal ON and OFF times. Duty cycle is the percentage of time during which stimulation occurs, calculated as stimulation time divided by the sum of signal ON and OFF times multiplied by 100. Stimulation time includes programmed ON time plus ramp-up and ramp-down periods of approximately 2 s each at frequencies above 10 Hz (Fig. 1).

Table 2 shows the duty cycle values for various combinations of ON and OFF times.

Signal ON time values range from 7 to 60 s. For signal OFF times, the range is 0.2–180 min (Table 3); setting OFF time to 0.0 min turns off the pulse generator. Stimulation with an ON time longer than OFF time (duty cycle >50%) has resulted in degenerative nerve damage in laboratory animals (26).

Duty cycle in clinical studies (Table 1)

Depression – In the D01 study (9), the initial programmed ON time was 30 s, followed by 5 min OFF. Physicians were permitted to change these settings during the first 2 weeks of the study, but only six patients (10%) were switched to a different stimulation schedule, in all cases 30 s ON followed by 3 min OFF. In the D02 study (13), the typical duty cycle at 3 and 12 months was 10%, with a median ON time of 30 s and a median OFF

Table 2 Duty cycle[1,2] values (%) for various ON and OFF times (25)

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

[1]Duty cycle is calculated by dividing stimulation time (programmed ON time plus 2 s of ramp-up time and 2 s of ramp-down time) by the sum of the ON time and OFF time.

[2]Italic values represent duty cycles higher than 50%, in which the ON time is greater than the OFF time. Stimulation with ON time greater than OFF time has resulted in degenerative nerve damage in laboratory animals (26). No comparable human data are available.

Table 3 Stimulation parameters for VNS therapy

Stimulation parameters	Programmable range	Programming steps	Recommended initial values	Typical target values
Output current	0–3.5 mA	0.25 mA	0.25 mA	1.0–2 mA
Frequency	1–30 Hz[1]	1, 2, 5, 10, 15, 20, 25, 30 Hz	20 Hz[2] 30 Hz[3]	20–30 Hz
Pulse width	130–1000 μs	130, 250, 500, 750, 1000 μs	250–500 μs	250–500 μs
Duty cycle	10–100%[4]	Function of signal ON, OFF times	10%	10%
Signal ON time	7–60 s	7, 14, 21, 30, 60 s	30 s	30 s
Signal OFF time	0.2–180 min[5]	5–60 min, 5-min steps 60–180 min, 30-min steps	5 min	5 min

[1]Values below 5 Hz should be avoided.

[2]In depression.

[3]In epilepsy.

[4]Duty cycles greater than 50% have resulted in nerve damage in laboratory animals (26).

[5]Setting OFF time to 0.0 min turns off the pulse generator.

time of 5 min. The ON time range was 7–30 s at 3 months and 7–60 s at 12 months, while the OFF time range was 0.20–180 min at 3 months and 0.30–180 min at 12 months.

Epilepsy – In the E05 study (14), VNS therapy for patients in the active stimulation group was programmed for the first 3 months as repeated cycles of 30 s ON followed by 5 min OFF (a 10% duty cycle). In the low-stimulation control group, cycles of stimulation were programmed as 30 s ON followed by 180 min OFF. At 1 month, mean ON time was 30 ± 0 s and mean OFF time was 5.0 ± 0.5 min. After 3 months, when physicians were free to change VNS therapy parameters for patients who continued in the long-term phase of the study, ON times remained at 30 s and OFF times could be changed from 5 min to 3, 1.8, or ≤ 1.1 min (10).

At 12 months, 53% of patients remained at OFF times of 5 min, but 47% of patients had been switched to OFF times ≤ 3 min (10). At 12 months, mean ON time had increased to 30.9 ± 13.7 s and mean OFF time had been reduced to 3.7 ± 2.3 min (14).

In a *post-hoc* analysis, DeGiorgio et al. (10) evaluated the effect of changes in OFF times on seizure frequency. While changes in OFF time did not significantly affect the response of the overall population, the 26 patients whose OFF time was reduced to ≤ 1.1 min after 3 months experienced a significant median reduction in seizures, from 21% at 3 months to 39% at 12 months ($P = 0.01$). While only 19% of patients had a response to VNS therapy at 3 months, 35% had a response at 12 months. In this group of patients, ON times ranged from 7 to 60 s and OFF times, from 12 to 66 s (a duty cycle of 22–58%). The authors examined other potential reasons for the significant increase in response among the patients with OFF times of ≤ 1.1, but found that neither changes in output current nor differences in the use of antiepileptic drugs had a significant effect on results. They noted that for some patients, OFF time was not the only variable that changed; the combined effects of reduced OFF time and increased output current may have affected the response of some patients. However, the effects of changes in output current were not specifically analyzed (10).

In the 2005 study of the effects of changes in stimulation parameters (11), the first treatment group had an ON time of 7 s and an OFF time of 18 s (44% duty cycle), the second group had 30 s ON and 30 s OFF (57% duty cycle), and the third group had 30 s ON and 3 min OFF (16% duty cycle). The primary finding was that all three duty cycles were equally effective in initial therapy. The percentage of patients with a 50% reduction in seizures was similar in all groups (31.6%, 31.7%, and 26.1%, respectively). In the treatment group with 30 s ON and 3 min OFF, 13% of patients experienced a 75% reduction in seizures, compared with 5.3% of patients in the 7 s ON, 18 s OFF group and none of the patients in the 30 s ON, 30 s OFF group (11).

In an evaluation of the effect of duty cycle on the rate of seizure reductions among registry patients, Labar (17) found that duty cycle was not associated with any significant difference in the degree of seizure rate decline from 3 to 12 months. However, as with any registry study, these findings should be interpreted with caution (17).

Safety and tolerability – Programmed ON time greater than OFF time has resulted in degenerative nerve damage in laboratory animals (26). As a result, therapy with ON times greater than OFF times is not recommended in clinical usage (22).

For patients with obstructive sleep apnea, prolonging OFF time may prevent exacerbation of apnea (27). In the study comparing three different duty cycles, all three treatment modes were well tolerated, and duty cycle did not appear to affect the rates of adverse events (11).

The external magnet

To supplement programmed stimulation in epilepsy, VNS therapy may be initiated by the patient on an *ad-hoc* basis. When an aura or the impending onset of a seizure is sensed, the patient or a companion can swipe a handheld magnet over the pulse generator to trigger an electrical stimulation. The magnet's activation current is set at a level that can be perceived by the patient, typically 0.25 mA higher than the normal daily programmed output current. In a 2001 study, Boon et al. (28) evaluated the use of magnets by patients and caregivers, concluding that the magnet is a useful tool that gives patients and caregivers an additional way to control seizures. However, caregivers rather than patients usually used the magnet because many patients were unable to anticipate a seizure. Because the study relied on self-reporting, the authors urged that results be interpreted with caution.

Experience with our own patients and their caregivers provides further insights into the benefits of magnet use. Patients and caregivers report a shortening of the seizure duration and a quicker recovery from seizures. They also note that they have a sense of empowerment because they feel that they can do something to control their seizures.

A magnet is not used to initiate stimulation in patients with depression because depression is not characterized by an identifiable event recognized by the patient (such as an aura or seizure in epilepsy) that might be modified by applying *ad-hoc* stimulation.

To temporarily discontinue programmed stimulation in either depression or epilepsy, a magnet may also be placed over the pulse generator and kept there for a duration determined by the patient. Patients are advised to use this function to avoid voice alteration when they plan to sing or speak in public, during eating if stimulation interferes with swallowing, or if stimulation becomes uncomfortable or painful (29, 30). For patients with epilepsy, the magnet may also be used to verify that the pulse generator battery is working (30); this function is not available for patients with depression because the magnet's output current setting is 0.0 mA (OFF) (29).

Setting therapeutic parameters

Many physicians begin stimulation as soon as the patient has recovered from surgery, usually after about 2 weeks. The VNS therapy trials for both pharmacoresistant epilepsy (2) and TRD (1) included a 2-week recovery period after surgery and before initiating stimulation, which is also recommended by the manufacturer (29). For some patients, it may be feasible to begin stimulation at subtherapeutic settings immediately after surgery by adjusting the output current to 0.25 mA in the recovery room. This strategy may be appropriate because it is easy for most patients and physicians to distinguish between side effects of surgery and those associated with stimulation. There is currently no way to predict the response of individual patients to particular parameter settings; current practice is gradual adjustment of stimulation parameters based on tolerability and effect on the patient.

Stimulation is started with low settings to develop tolerance in previously untreated nerves (Table 3). After 2 weeks, the current can be increased by 0.25–0.5 mA at 2-week intervals until the patient is at a higher tolerated output current, typically ranging from 1.0 to 2.0 mA. Within that range, the upper limit of the output current is the maximum level that the individual patient can tolerate (Table 4).

System diagnostics (a lead test) are generally not performed until the patient is accustomed to an output current of 1.0 mA or greater. The test may take 30 s or more; applying 1.0 mA of current to a previously untreated nerve is likely to be uncomfortable for the patient. In addition, the risk of asystole described by Asconape et al. (20) and Ben-Menachem (21) in operating-room settings may be present whenever a previously untreated nerve is stimulated with an output current of 1.0 mA or greater.

If the patient does not respond to VNS therapy at the maximum tolerable output current after 1–3 months in epilepsy or 6–12 months in depres-

Table 4 Suggested sequence of parameter adjustments

To increase efficacy	To manage side effects
1. ≥2 weeks after implant, increase output current by 0.25–0.5 mA at 2-week intervals to maximum tolerated level, typically 1.0–2.0 mA.	1. Reduce output current 2. Reduce pulse width 3. Reduce frequency 4. Reduce ON time
2. If no response after 1–3 months at maximum tolerated output current, gradually increase duty cycle (increase ON time, decrease OFF time)	

sion, the duty cycle may be increased by gradually adjusting the ON and OFF times. As the duty cycle increases, it may be appropriate to reduce the pulse width or output current to minimize side effects (23). It is difficult to evaluate the effects of changing the ON and OFF times in patients with depression. There are few studies of variation of ON and OFF times, and the effects of VNS therapy in depression are highly dependent on the duration of therapy. Patients with TRD who do not respond initially to therapy are more likely to respond to the continuation of therapy for additional months at the same parameters than they are to respond immediately to a change in ON and OFF times. For some selected patients with epilepsy, an increased duty cycle may be the most successful approach, as shown in the DeGiorgio et al. study (11).

Every setting change presents a tradeoff among the objectives of improved efficacy, better tolerance, and battery life. Reduction of output current or pulse width may improve tolerability for patients who experience hoarseness, coughing, or dyspnea. A duty cycle with briefer ON and OFF times may be better tolerated, although this higher duty cycle may drain the battery more quickly. As is the case with antidepressant or antiepileptic drugs, VNS therapy must be adjusted in a gradual and systematic fashion, individualizing therapy for each patient to optimize efficacy and minimize side effects.

In clinical practice, it may take time for patients to experience a response to VNS therapy. In the D01 study (9), mean Hamilton Rating Scale for Depression 28 ($HAM\text{-}D_{28}$) scores continued to decline over the course of the study for patients who experienced a treatment response; the median time to the first response for those patients was 45.5 days. In the study of long-term treatment of epilepsy (10), median response rates improved between 3 and 12 months for all treatment groups. Morris et al. (18) noted a plateau at 2 years for patients with epilepsy. In both epilepsy and depression, the treatment effect increases with time.

Battery life and device removal

For the models 102 and 102R pulse generators, the approximate predicted battery lifetime is 8.4 years (100.8 months) at programmed settings of 20 Hz with a 500 μs pulse width, 2 mA output current, 4 kΩ lead impedance, and 10% duty cycle (22). If the duty cycle were changed to 50% (60 s ON, 60 s OFF), the nominal battery life would be 2.6 years (22). Battery life is shortened as output current, pulse width, frequency, and duty cycle are increased. The physician should conduct a system diagnostic test at least every 6 months to determine whether the device is operating within normal parameters; abnormal values may indicate a problem with a lead (such as a lead fracture, fibrosis between the nerve and the electrode, or lead disconnection from the pulse generator) or high battery impedance as the battery approaches the end of service (22).

It may occasionally be necessary to remove the pulse generator and leads from a patient in whom they have been implanted. Removal may be required if an infection occurs at the implant site, if the system malfunctions, or if lead fracture occurs. [The survival rate for the Model 300 lead is 96.9% at 5 years (31).] In these cases, a new pulse generator and lead are implanted to minimize the risk of infection. A single series of cases has been reported suggesting it might be possible to attach a replacement lead to the right vagus nerve. The physician may also decide to remove the pulse generator and leads if the patient does not respond to or cannot tolerate VNS therapy despite attempts to adjust parameter settings. Microsurgical procedures have been described for the successful removal or revision of leads without apparent damage to the vagus nerve (32, 33).

Discussion

The use of VNS therapy to treat patients with depression requires the participation of several specialists to ensure the best outcomes. The psychiatrist makes a diagnosis and determines that the patient is a candidate for VNS therapy after four or more antidepressants have proven ineffective in adequate trials. Prior use of ECT should not be considered a contraindication to a requirement for the use of VNS therapy. The implant procedure should be performed by a surgeon accustomed to working in the area of the vagus nerve and familiar with its anatomy, particularly the cardiac branches. After the procedure, some psychiatrists may wish to consult a neurologist or epileptologist experienced in the use of VNS therapy. Conferring with representatives of the device manufacturer may also be useful.

Much remains to be learned about the use of VNS therapy in depression and epilepsy. Although VNS therapy has been effective for TRD and pharmacoresistant epilepsy when other treatments have failed, as with all other treatments, VNS therapy is not effective for all patients. The interactions among output current, pulse width, frequency, and duty cycle have not been fully characterized, and it is possible that some as-yet-unidentified variable could be responsible for differences in treatment effect. In addition, the clinical studies of parameters

used in VNS therapy are limited by small sample sizes, variations among patient characteristics, and in some cases, lack of sham-treatment controls. With those limitations in mind, this article attempts to present all available data and recommendations based on experience to assist clinicians in optimizing therapy for their patients.

Additional studies are needed to identify the patient-related factors that predict response to therapy and the parameter settings that are most effective for patients with various disease characteristics. The data from clinical studies of VNS therapy provide a good foundation for initiating VNS therapy and adjusting parameter settings.

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References

1. Rush AJ, Marangell LB, Sackeim HA et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry 2005;**58**:347–54.
2. Handforth A, DeGiorgio CM, Schachter SC et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998;**51**:48–55.
3. Cyberonics Inc. (May 25, 2006) Cyberonics Reports Fiscal 2006 Financial Results. Press Release. Available at: http://www.cyberonics.com/PressRelease_detail.asp?ID=EFC0356F-F219-41B3- 8E5C-A6B0243CC7CD. Accessed June 22, 2006.
4. Cyberonics Inc. (August 22, 2005) Cyberonics' VNS Therapy Surpasses 100,000 Patient Years of Experience. Press Release. Available at: http://www.cyberonics.com/PressRelease_detail.asp?ID=D42A2040-0C36-4E9F-9FC5-41E07E7EF1B3. Accessed June 22, 2006, 2005.
5. George MS, Nahas Z, Bohning DE et al. Vagus nerve stimulation therapy: a research update. Neurology 2002;**59**(Suppl. 4):S56–61.
6. Krahl SE, Senanyake SS, Handforth A. Seizure suppression by systemic epinephrine is mediated by the vagus nerve. Epilepsy Res 2000;**38**:171–5.
7. Labiner D, Schwirtz D, Ahern G, MacDonald J, Weinand M. Shorter pulse width of vagus nerve stimulation is as effective in reducing seizure frequency as standard stimulation and is better tolerated. Epilepsia 1999;**40**(Suppl. 7):141.
8. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. Lancet Neurol 2002;**1**:477–82.
9. Sackeim HA, Rush AJ, George MS et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. Neuropsychopharmacology 2001;**25**:713–28.
10. DeGiorgio CM, Thompson J, Lewis P et al. Vagus nerve stimulation: analysis of device parameters in 154 patients during the long-term XE5 study. Epilepsia 2001;**42**:1017–20.
11. DeGiorgio C, Heck C, Bunch S et al. Vagus nerve stimulation for epilepsy: randomized comparison of three stimulation paradigms. Neurology 2005;**65**:317–9.
12. Rush AJ, George MS, Sackeim HA et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. Biol Psychiatry 2000;**47**:276–86.
13. Rush AJ, Sackeim HA, Marangell LB et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. Biol Psychiatry 2005;**58**:355–63.
14. DeGiorgio CM, Schachter SC, Handforth A et al. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia 2000;**41**:1195–200.
15. 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.
16. Liporace J, Hucko D, Morrow R et al. Vagal nerve stimulation: adjustments to reduce painful side effects. Neurology 2001;**57**:885–6.
17. Labar D. Vagus nerve stimulation for 1 year in 269 patients on unchanged antiepileptic drugs. Seizure 2004;**13**:392–8.
18. Morris GL III, Mueller WM, and the Vagus Nerve Stimulation Study Group. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01–E05. Neurology 1999;**53**:1731–5.
19. Tatum WO IV, Moore DB, Stecker MM et al. Ventricular asystole during vagus nerve stimulation for epilepsy in humans. Neurology 1999;**52**:1267–9.
20. Asconape JJ, Moore DD, Zipes DP, Hartman LM, Duell WH Jr. Bradycardia and asystole with the use of vagus nerve stimulation for the treatment of epilepsy: a rare complication of intraoperative device testing. Epilepsia 1999;**40**:1452–4.
21. Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. J Clin Neurophysiol 2001;**18**:415–8.
22. Cyberonics Inc. Physician's Manual VNS Therapy™ Pulse Model 102 Generator and VNS Therapy™ Pulse Duo Model 102R Generator (Houston, Texas, Cyberonics Inc). Available at: http://www.vnstherapy.com/epilepsy/hcp/Manuals/default.aspx. Accessed June 22, 2006, 2003.
23. Heck C, Helmers SL, DeGiorgio CM. Vagus nerve stimulation therapy, epilepsy, and device parameters: scientific basis and recommendations for use. Neurology 2002;**59**(Suppl. 4):S31–7.
24. Woodbury DM, Woodbury JW. Effects of vagal stimulation on experimentally induced seizures in rats. Epilepsia 1990;**31**(Suppl. 2):S7–19.
25. Cyberonics Inc. Depression Physician's Manual VNS Therapy™ Pulse Model 102 Generator and VNS Therapy™ Pulse Duo Model 102R Generator (U.S. Domestic Version) (Houston, Texas, Cyberonics Inc). Available at: http://www.vnstherapy.com/depression/hcp/Manuals/default.aspx. Accessed June 22, 2006, 2005.
26. Agnew WF, McCreery DB. Considerations for safety with chronically implanted nerve electrodes. Epilepsia 1990;**31**(Suppl. 2):S27–32.
27. Malow BA, Edwards J, Marzec M, Sagher O, Fromes G. Effects of vagus nerve stimulation on respiration during sleep. Neurology 2000;**55**:1450–4.

28. Boon P, Vonck K, Van Walleghem P et al. Programmed and magnet-induced vagus nerve stimulation for refractory epilepsy. J Clin Neurophysiol 2001;**18**:402–7.
29. Cyberonics Inc. Depression Patient's Manual For Vagus Nerve Stimulation with the VNS Therapy™ System (Houston, Texas, Cyberonics Inc). Available at: http://www.vnstherapy.com/depression/hcp/Manuals/default.aspx. Accessed June 22, 2006, 2005.
30. Cyberonics Inc. Epilepsy Patient's Manual for Vagus Nerve Stimulation with the VNS Therapy™ System (Houston, Texas, Cyberonics Inc). Available at: http://www.vnstherapy.com/epilepsy/hcp/Manuals/default.aspx. Accessed June 22, 2006, 2005.
31. Cyberonics Inc. Data on file.
32. Espinosa J, Aiello MT, Naritoku DK. Revision and removal of stimulating electrodes following long-term therapy with the vagus nerve stimulator. Surg Neurol 1999;**51**:659–64.
33. MacDonald J, Couldwell WT. Revision of vagal nerve stimulator electrodes: technical approach. Acta Neurochir 2004;**146**:567–70.