Chronic Vagus Nerve Stimulation Improves Alertness and Reduces Rapid Eye Movement Sleep in Patients Affected by Refractory Epilepsy

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Objective: Our study aimed to evaluate the existence and entity of changes in sleep structure following vagus nerve stimulation in patients with refractory epilepsy.

Method: A polysomnographic study was performed on the nocturnal sleep of 10 subjects with refractory epilepsy. Subjects were recorded both in baseline conditions and after chronic vagus nerve stimulation. Sleep parameters of the entire night were evaluated. Mean power value of slow-wave activity was computed in the first non-rapid eye movement sleep cycle. A sleep-wake diary evaluated quantity of both nocturnal and daytime sleep, while visual-analog scales assessed quality of sleep and wake. The differences between the 2 conditions underwent parametric and nonparametric statistical evaluation.

Results: Vagus nerve stimulation determines a significant reduction of REM sleep (in all subjects with vagus nerve stimulus intensity greater than 1.5 milliampere, but not in the only patient with a stimulus intensity less than 1.5 milliampere, along with an increase in the number of awakenings, percentage of wake after sleep onset, and stage 1 sleep. Data from a sleep-wake questionnaire show a decrease in both nocturnal sleep and daytime naps and an increased daytime alertness, while the quality of wakefulness is globally improved. Spectral analysis shows an enhancement of delta power during non-rapid eye movement sleep.

Conclusions: Our data demonstrate major effects of vagus nerve stimulation on both daytime alertness (which is improved) and nocturnal rapid eye movement sleep (which is reduced). These effects could be interpreted as the result of a destabilizing action of vagus nerve stimulation on neural structures regulating sleep-wake and rapid eye movement/non-rapid eye movement sleep cycles. Lower intensity vagus nerve stimulation seems only to improve alertness; higher intensity vagus nerve stimulation seems able to exert an adjunctive rapid eye movement sleep-attenuating effect.

Key Words: sleep, REM sleep, epilepsy, alertness, vagus nerve stimulation, slow wave activity, mood disorders

INTRODUCTION

VAGUS NERVE STIMULATION (VNS) IS A METHOD THAT HAS BEEN EXTENSIVELY APPLIED FOR ABOUT 10 YEARS AS AN ADD-ON THERAPY IN EPILEPTIC PATIENTS REFRACTORY TO EITHER PHARMACEUTICAL OR SURGICAL TREATMENT. Data on its efficacy were recently reviewed.[1-4] The method was recently proposed and tested as a therapeutic tool for drug-resistant depression.[5-7] Using the Epworth Sleepiness Scale and Multiple Sleep Latency Test (MSLT), Malow et al[8] recently reported a reduced daytime sleepiness in epileptic patients.

Mechanisms underlying the effects of VNS on epilepsy, mood, and vigilance are not entirely clear. Via the nucleus tractus solitarius, the vagus nerve projects to many brainstem regions, including the parabrachial nucleus (PBN) and locus coeruleus (LC). Via the PBN, it has widespread connections with thalamus, basal forebrain, hypothalamus, and cerebral cortex.[9,10] Given these connections, it is reasonable to expect an influence of VNS on alertness and sleep. Experimental data provide evidence that VNS can promote both wakefulness and rapid eye movement (REM) sleep, via the balance between cholinergic and noradrenergic connections.[1,11,12] Only a few studies on nocturnal sleep in VNS have been performed in humans. Malow et al found no changes with low-intensity (<1.5 milliamperes [mA]) VNS.[8] A short abstract[13] reports a significant decrease in total REM sleep time in a group with high-intensity, high-frequency VNS and either no change or an increase in REM in another group with low-frequency, low-intensity VNS.

Given the role of brainstem regions in the control of wakefulness and REM sleep, we postulate that VNS may affect the balance between wake and REM sleep, with possible different outputs modulated by its intensity. In order to test this hypothesis, we compared nocturnal sleep polysomnographic features, intensity of non-REM (NREM) sleep as measured by means of slow wave activity (SWA) power spectra, and daytime alertness in a sample of epileptic patients before and after chronic VNS with a wide range of stimulus intensities.

METHODS

Subjects and VNS

Ten subjects (age range, 22-43 years) with a diagnosis of refractory epilepsy made on the basis of their clinical history and diagnostic data (electroencephalogram [EEG], computed tomography, nuclear magnetic resonance imaging) participated in the study. Demographics and clinical features of patients are given in Table 1; 4 subjects presented severe cognitive impairment due to previous encephalopathy. All patients received pharmacologic polytherapy (Table 1). Patients were asked to sign an informed consent; for those with severe cognitive impairment, informed consent was provided by their caregivers (usually parents). None of the subjects included in the study reported a history of specific sleep disorders; all of them reported habitual daytime naps. None of the subjects could cope with a daily job.

The VNS device (NCP System; Cyberonic, Houston, TX, USA) was implanted according to the established guidelines.[1] The VNS titration was performed and based on frequency of seizures and subjective toler-

Table 1—Patient demographics and clinical features

Patient	Sex	Age (years)	History	Seizures	Drug therapy	VNS intensity (mA)	VNS on-time/ off-time	Reduction in seizures, %
1	M	27	Infantile encephalitis	G	CBZ/DZP	2.5	60 s /5 min	50
2	M	25	Infantile encephalitis	G	CBZ/VPA/ CZP/TPM	2.25	30 s /5 min	80
3	F	22	Infantile encephalitis	G	VPA/CZP/ PhB/LMT	2.5	30 s /5 min	50
4	F	37	Tuberous sclerosis	PC	VBT/DPH/ PhB/VPA/ CZP	2	60 s/5 min	30
5	F	36	Encephalitis	PC	CBZ	1.25	60 s /3 min	70
6	F	42	Unknown	A+p	CLO/CBZ/ PhB	3.25	60 s /3 min	50
7	F	34	Unknown	PC	PhB/CBZ/ PhB/LMT/ TPM	2	60 s /3 min	0
8	F	37	Unknown	G	DNT/CBZ/ VPA/GPN	1.75	60 s /3 min	30
9	F	43	Head trauma	PC	DNT/PhB/ CBZ/BBC	2	30 s /5min	50
10	M	38	Unknown	G	CBZ/VBT/ LMT/PhB	2.5	60 s /3 min	30

VNS, vagus nerve stimulation; *Drug therapy*: **CBZ**, Carbamazepine; **DZP**, Diazepam; **VPA**, Valproic acid; **CZP**, Clonazepam; **TPM**, Topiramate; **PhB**, Phenobarbital; **LMT**, Lamotrigine; **VBT**, Vigabatrine; **DPH**, diphenylhydantoin; **CLO** Clobazam; **GPN**, Gabapentine; **BBC**, Barbexaclone *Seizures*: **G**, generalized; **PC**, partial complex; **A+P**, atonic plus partial

Table 2—Sleep parameters

Sleep parameters	Baseline, mean ± SD	Treatment, mean ± SD	P
Sleep latency, min	12.44 ± 8.97	10.33 ± 6.22	0.489
REM latency, min	97.11 ± 38.41	124.78 ± 58.48	0.353
Total, min	23.78 ± 25.32	89.78 ± 84.29	0.036
WASO, %	5.33 ± 6.06	22.89 ± 22.17	0.038
Total sleep time, min	415.22 ± 41.05	315.22 ± 140.72	0.071
Sleep efficiency, %	88.78 ± 6.91	70.11 ± 24.60	0.066
REM, min	77.33 ± 36.24	27.33 ± 19.81	0.006
REM, %	18.44 ± 7.65	7.56 ± 3.91	0.004
REM episodes, n	3.13 ± 0.35	1.63 ± 1.3	0.01
Stage 1, min	14.89 ± 11.71	27.11 ± 14.81	0.001
Stage 1, %	3.67 ± 3.04	11.22 ± 12.05	0.054
Stage 2, min	225.55 ± 64.90	191.67 ± 98.47	0.191
Stage 2, %	54.78 ± 15.47	55.22 ± 15.55	0.900
Stage 3+4, min	96.67 ± 60.55	79.44 ± 50.39	0.488
Stage 3+4, %	22.89 ± 13.40	25.78 ± 15.59	0.573
Awakenings, n	9.89 ± 7.77	21.11 ± 11.43	0.007
Arousals, n	21.56 ± 12.05	28.67 ± 17.09	0.26
Stage shifts, n	107.44 ± 87.77	130.22 ± 76.15	0.526

REM, rapid eye movement sleep; WASO, wake after sleep onset

Table 3—Results from the analysis of the sleep-wake diary data

Parameter	Mean score before VNS	Mean score after VNS	P
Sleep quantity			
Total sleep time, min	517 ± 58.3	462 ± 25.3	0.037
Daytime naps, min	96.5 ± 55.4	54.5 ± 25.2	0.021
Sleep quality			
Easy awakening	2.47 ± 0.38	7.25 ± 2.6	0.0003
Daytime Alertness			
at 10 am	6.33 ± 1.37	8.56 ± 1.72	0.034
at 2 pm	5.81 ± 1.04	8.24 ± 1.79	0.012
at 9 pm	5.4 ± 1.51	8.26 ± 1.19	0.006
Wake quality			
Attention	3.36 ± 1.46	8.21 ± 2.17	0.0001
Mood	3.55 ± 0.77	7.12 ± 1.69	0.0001
Quality of life	3.42 ± 1.69	6.52 ± 1.22	0.0002

ance. Stimulus intensity ranged from 1.25 mA to 3.25 mA, with a stimulation frequency of 30 Hz and a pulse width of 250 milliseconds to 500 milliseconds. Intensity and on-time/off-time intervals varied from patient to patient and are reported in Table 1. The VNS device was activated throughout the whole day and night.

Since patients presented neither increase in ictal events, nor toxicity, antiepileptic drugs were maintained at a constant dosage for the entire duration of the study.

Before the VNS device was implanted, the clinical state of patients was assessed on the grounds of a 3-month report of the number of seizures. A baseline polysomnography (PSG) was performed and preceded by 1 night of adaptation. Although initially envisioned, the severe cognitive impairment of some of the patients made impossible a completion of an MSLT for an objective assessment of daytime sleepiness. Likewise, a subjective assessment by the Epworth Sleepiness Scale was unreliable because the lifestyle of most of the patients did not comply with the items in the scale. An ad hoc sleep-wake diary allowed the quantitative (minutes) evaluation of nocturnal and daytime sleep. Sleep quality, daytime sleepiness, and quality of wakefulness were assessed by visual-analog scales (ranging from 0 to 10 centimeters, where 0 was assigned to the lowest qualitative feature, while 10 to the highest qualitative feature) given to either patients or their caregivers. These data were collected for 10 days before PSG. A mean period of 13.7 ± 3.8 months passed before implantation of the VNS, after which the procedure was repeated. One subject was deemed not eligible for the study due to the high number of EEG alterations, which made proper sleep-stage scoring unreliable in both baseline and treatment conditions.

Polysomnographic Recordings

The PSGs were performed on a 32-channel computerised EEG system (EBINeuro Galileo NT). Recording started at 11:00 PM and stopped at 7:00 AM. The EEG was acquired in physical reference with successive reconstruction of bipolar derivations from 16 electrodes (F2, F1, F4, F3, C4, C3, P4, P3, O2, O1, F8, F7, T4, T3, T6, T5) placed according to the 10-20 international system. The low-pass filter was set at 70 Hz with the high-pass filter at 0.5 Hz. Sensitivity was set at 10 µV/mm. The notch filter was switched on. Furthermore, electrooculograms, submental electromyography (EMG), nasal airflow, respiratory effort, electrocardiogram, pulse oximetry, anterior tibialis EMG, and VNS signal were recorded. The VNS signal was obtained by 1 electrode applied nearby the VNS device, in order to mark the on-time and off-time intervals of the device on a single channel.

All signals were sampled with 512-Hz frequency and 12-bit resolution and stored with 128-Hz frequency and 8-bit size, after the application of an antialiasing digital filter. Sleep parameters were scored according to Rechtschaffen and Kales[14] criteria, and each hypnogram was stored as digital data. In order to evaluate possible sleep-fragmenting influences exerted by the onset of the VNS device, the temporal relationship between VNS onset and arousals, awakenings, and backward phase shifts occurring within 10 seconds were visually explored and recorded.

Arousals were recognized automatically by a specific software program,[15] then manually inspected and revised; the arousal index was computed for each recording.

Electroencephalographic Spectral Analysis

The digitized EEG, derived from channel C4-P4, was assessed in each subject (Sande-Tukey decimation in frequency Fast Fourier Transform algorithm) for 2-second consecutive epochs and preprocessed by a Tukey window; the resulting spectra were averaged every 1 minute. Channel C4-P4 was chosen because it was less affected by epileptogenic

discharges and EEG alterations in most patients.

Power spectra segment corresponding to delta (ie, SWA- 0.5-4.0 Hz) was assessed. Mean absolute values of SWA were computed for the descending branch of the first NREM sleep cycle (from the first spindle to the first epoch of stage 4 sleep). Epochs containing artifacts, epileptogenic discharges, arousals, and wakefulness after sleep onset were carefully discharged.

Statistical Analysis

Data obtained after the implantation of VNS were compared to data obtained before VNS by applying a paired *t*-test independently of each variable, fixing α at the 0.05 level. This procedure was applied to the 3 groups of variables: data from the hypnogram, SWA, and the values derived from the questionnaire. The SWA values underwent logarithmic transformation.
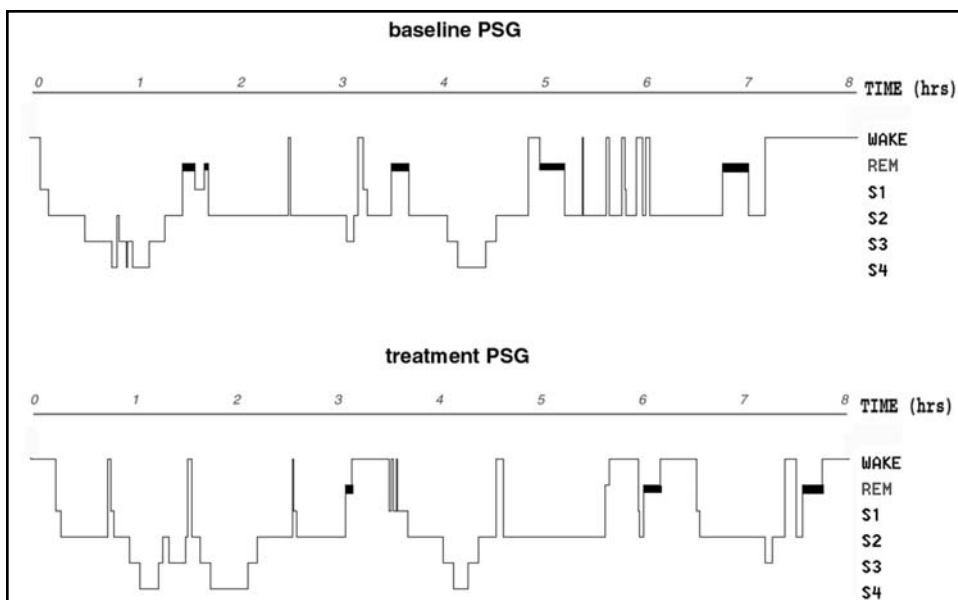

Figure 1—Hypnograms of a representative subject (patient 2) before (baseline polysomnography) and after vagus nerve stimulation (treatment polysomnography). Note rapid eye movement sleep reduction, both in duration and number of episodes, and its replacement with wake episodes. Non-rapid eye movement sleep is substantially unaffected. PSG, polysomnography; REM, rapid eye movement sleep; S1, stage 1 sleep; S2, stage 2 sleep; S3, stage 3 sleep; S4, stage 4 sleep.
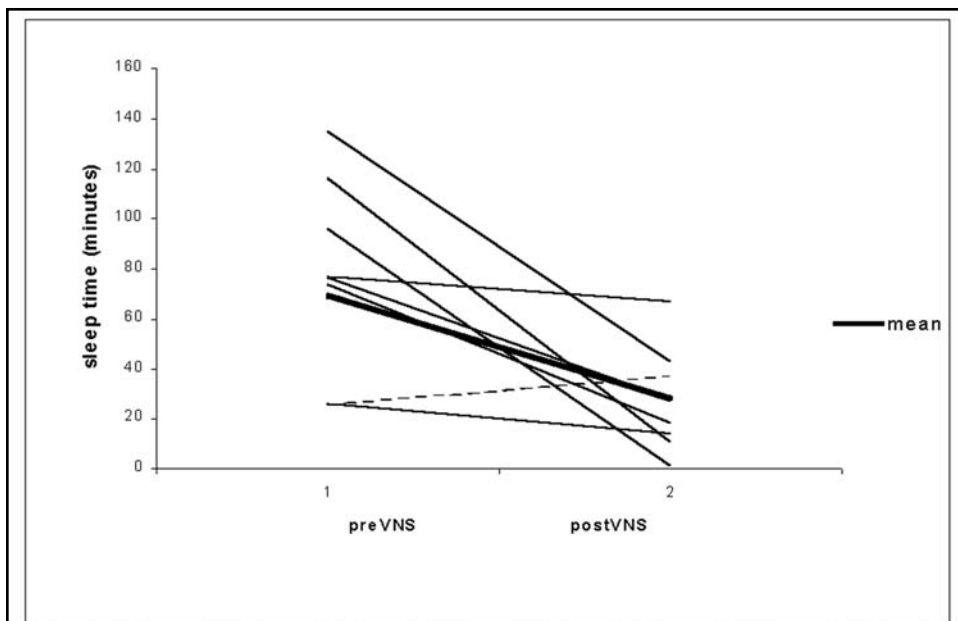

Figure 2—Comparison of duration of rapid eye movement sleep between baseline and treatment polysomnography. Note the decrease of rapid eye movement sleep in all subjects except patient 5, whose vagus nerve stimulation intensity was lower. VNS, vagus nerve stimulation.

The hypothesis of a cooccurrence, within 10 seconds, between VNS onset and arousals, awakenings, or backward phase shifts was investigated by means of a χ^2-test. The threshold for the rejection of the null hypothesis was set at 0.05.

Correlation between significant changes, VNS intensity, and reduction of epileptic seizures was verified by means of linear regression tests.

RESULTS

Nine subjects completed the study. No patient showed obstructive apneas, oxygen desaturation, or periodic limb movements during the baseline PSG recording. No epileptogenic seizures were recorded either during baseline or during treatment PSG.

Clinical Outcome

Data from the 3-month reports about the number of seizures before VNS-device implantation and in the 3-month period before the treatment PSG showed a remarkable reduction of seizure frequency after VNS implantation, ranging from 30% to 80% (mean value: 44% ± 23 %) in all subjects but 1 (patient 7), who showed no changes. Data for each subject are reported in Table 1.

Sleep Parameters

Statistically significant differences between means were found in the following parameters: number of awakenings, wakefulness after sleep onset ([WASO] in both duration and percentage), and stage 1 sleep increased with chronic VNS, while REM sleep (duration, percentage, and number of episodes) decreased (Table 2, Figures 1 and 2).

A significant correlation between VNS intensity and modification of sleep parameters was not found. Nevertheless it's worth noting that a decrease of REM sleep occurred in all patients except the 1 whose stimulation intensity was less than 1.5 mA (Figure 2).

No significant temporal relationship between VNS onset and appearance of arousals, awakenings, or backward phase shifts was found. (The occurrence of their concomitance was not significantly higher than occurrence by chance.)

No significant changes in breathing during sleep were reported during the second PSG.

Spectral Analysis

A significant power increase was found for SWA (0.5-4.0 Hz) during NREM sleep (mean ± SD 33.65±28.33 vs. 48.93±35.23 μV²; $P < 0.01$).

Sleep-Wake Diary

Subjective data derived from our sleep-wake diary showed significant differences after chronic VNS. A decrease in both nocturnal sleep and daytime naps was found. Furthermore, patients reported an easier awakening in the morning. Daytime sleepiness was notably reduced in the morning, afternoon, and evening sessions. Parameters regarding the quality of wakefulness seemed to be globally

improved; data reports concerning attention, mood, and quality of life showed a sensible improvement (Table 3). A trend towards a significant correlation between VNS intensity and reduction of sleep over 24 hours (P=0.056), and between VNS intensity and reduction of nocturnal sleep (P=0.066), was found.

DISCUSSION

On the whole, our data propose a picture of a shortened nocturnal sleep with increased wakefulness during both the night and the day, without any sign of worsening of daytime alertness. Moreover, patients do not perceive their sleep as less restorative, and, furthermore, they report an easier awakening and an increased subjective daytime alertness. In our opinion, the increase of WASO and of the number of awakenings in nocturnal sleep are only apparently suggestive of a worsening in sleep quality. All other parameters related to sleep initiation and maintenance, build up, and representation of slow wave sleep are unchanged. Sleep onset is not delayed, and the number of stage shifts and arousals are substantially unaffected, thus ruling out an augmented sleep fragmentation. The possibility of sleep disruptions by a nonspecific effect of the stimulation (eg, a physical sensation) can be reasonably ruled out by the lack of coincidence between the stimulus–on signal and microstructural events related to sleep disruption, such as arousals and backward phase shifts. Moreover, slow sleep (stages 3 and 4) as a whole, as well as the proportion of the lightest NREM sleep (Stage 2), remain unchanged. The SWA (delta power) is increased, and confirms data reported by Armitage.[16,17] The SWA is considered a measure of sleep depth homeostatically related to the duration of prior wakefulness[18]; its increase in our patients could therefore be considered as a restorative compensation of the shortening of sleep. Our main finding is that VNS reduces the number of REM-sleep episodes and its duration, enhancing wakefulness. In this framework, the increase of WASO and of the number of awakenings can be seen as a mere replacement of REM episodes with wakefulness periods (Figure 1).

Our data are in good agreement with those previously reported by Meloche et al[19] and confirmed by means of objective MSLT measures and a scale validated by Malow et al.[8] Sleep reduction and alertness improvement were not correlated with the VNS attenuating effect on seizures, while a trend towards a statistically significant correlation between sleep reduction and VNS intensity was found. Concerning the effects of VNS on REM sleep, experimental studies in cats and rats reported an enhancement of pontogeniculooccipital wave density and an increase of total amount of REM sleep after VNS, though obtained by a stimulus intensity able to evoke relevant behavioral and autonomic responses.[11,12] Malow et al reported no change in overnight sleep parameters, at least in those patients treated with VNS and a stimulus intensity below 1.5 mA.[8] Moreover, they observed an increase in the number of daytime naps that contained REM sleep[8]; Vaughn described a decreased nocturnal REM sleep in patients with high-intensity, high-frequency stimulation, while-low intensity, low-frequency stimuli either increased or did not change total REM duration.[13]

Regarding VNS effects on REM sleep, taking our sample together with data from the literature, both facilitating and inhibiting effects are found. A hypothesis can be made in light of neuroanatomic and functional connections of the vagus nerve.

Saper[20] has postulated the existence of a bistable hypothalamic sleep-wake switch system, elaborating a model in which several functional structures are linked by a complex balance of reciprocal inhibition and facilitation: REM-on/REM-off neurons (contained in the LC[20-24] and PBN[25-28]), the sleep promoting ventrolateral preoptic (VLPO) nuclei [29,30,31] and the wake-promoting orexin neurons[32-34] seem to be involved in this system (see also Pace-Schott and Hobson for an extensive review of the literature[35]).

Afferents in the vagus nerve project to the nucleus of the solitary tract. Most of the output is relayed by the PB, which in turn projects to several structures, including the LC,[36,37] VLPO, [37] and the orexin neurons.[38-42]

It could be hypothesized that VNS, through its connection to these structures, could act as a destabilizing factor. Low stimulation might provide an increase in arousing influences, thus promoting wakefulness and, to a smaller extent, REM sleep[8,13]; higher-intensity stimulus might cause a relatively augmented excitatory orexin input. The increased arousal influences and the decreased activity of the extended VLPO could thus allow earlier and more frequent transitions from REM sleep to wakefulness.

A mean reduction in seizure frequency of about 40% was found in our sample, which confirms current reports in the literature.[4] The REM-attenuating effect of VNS that we found could also be linked to its seizure-reducing effects. Although the neuronal mechanism underlying the anticonvulsant efficacy of VNS has not yet been elucidated, a major role seems to be played by the LC. A positive link between VNS and the LC has been demonstrated[36,43] both with c-*fos* activation after VNS and electrophysiologically.[44] Either an LC lesion, or its inactivation by lidocaine, reverses the seizure-attenuating effects of VNS, thus suggesting that the noradrenergic system is an important part of the anticonvulsant effect. Results of these studies are consistent with the hypothesis that the LC can mediate both induced seizure reduction and REM-sleep attenuation.

Vagus nerve stimulation has been proposed and successfully used for treatment of resistant depression, on the basis of positive mood effects observed in patients with epilepsy.[5] Moreover, clinical and animal studies indicate that VNS effects result in changes in neurotransmitters implicated in major depression, chiefly norepinephrine. Vagus nerve stimulation activates the LC, the main source of brain norepinephrine. Since many of the current therapies for depression are believed to work using the same neurotransmitter, it has been hypothesized that VNS might also have antidepressant effects.[6,7] Although our study was not designed to investigate mood-related parameters, a mood improvement and an enhancement of quality of life can be noticed when examining our questionnaire results. These effects are not correlated with the reduction in seizure frequency and confirm data by Dodrill and Morris.[45]

Our data on selective REM reduction, operated by VNS, offer another link between antiepileptogenic and antidepressive effects due to the well-known antidepressant properties of REM-sleep deprivation.

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