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# Vagus nerve stimulation for refractory epilepsy

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Vagus nerve stimulation (VNS) is a neurophysiological treatment for patients with medically or surgically refractory epilepsy. Since the first human implant in 1989, more than 10 000 patients have been treated with VNS. Two randomized controlled studies have shown a statistically significant decrease in seizure frequency during a 12-week treatment period versus a baseline period when 'high stimulation' mode was compared with 'low stimulation' mode. The efficacy appears to increase over time. In general, one third of the patients show a >50% reduction of seizure frequency; one third show a 30–50% seizure reduction, and one third of patients show no response. Few patients become seizure-free. Side effects during stimulation are mainly voice alteration, coughing, throat paraesthesia and discomfort. When studied on a long-term basis, VNS is an efficacious, safe and cost-effective treatment not only in adults but also in children and the elderly. The precise mechanism of action remains to be elucidated. In recent years much progress has been made through neurophysiological, neuroanatomical, neurochemical and cerebral blood flow studies in animals and patients treated with VNS. Further elucidation of the mechanism of action of VNS may increase its clinical efficacy and our general understanding of some physiopathological aspects of epilepsy. Finally, VNS may become an alternative treatment for other conditions such as depression and pain.



*Key words:* refractory epilepsy; vagus nerve stimulation; mechanism of action; efficacy; safety; cost-benefit.

## INTRODUCTION

Epilepsy is the second most common chronic neurological disorder after stroke affecting approximately 0.5–2% of the population[1]. Seventy percent of patients can be successfully treated with one or more antiepileptic drugs (AEDs). Despite adequate antiepileptic treatment 30% of patients continue to have seizures or experience unacceptable pharmacological side effects[2]. For these patients with 'medically refractory' epilepsy, epilepsy surgery is a therapeutic alternative. Resective surgery is a curative therapy when the epileptogenic zone can be identified and renders 60–90% of patients seizure free[3]. Pre-surgical evaluation requires a thorough patient selection and in a substantial number of patients the epileptogenic zone cannot be identified or is located in a functional brain area. Unsuitable candidates for resective surgery have few options left. Administration of a new AED will lead to seizure freedom in a maximum of 7% of patients[4]. Electrical stimulation of the vagus nerve is an efficacious neurophysiological treatment for patients with refractory epilepsy who are unsuitable candidates for curative resective surgery or who have experienced insufficient benefit from such a treatment.

## HISTORY

The first vagus nerve stimulator was implanted in humans in 1988. However, the historical basis of peripheral stimulation for treating seizures dates back to centuries ago. In the sixteenth and seventeenth century physicians described the use of a ligature around the limb in which a seizure commences to arrest its progress. This method is due to Pelops for whom this observation was proof that epileptic fits originated from the limb itself. This hypothesis was reviewed in the beginning of the nineteenth century when Odier[5] and also Brown-Séquard showed that ligatures are equally efficacious in arresting seizures caused by organic brain disease e.g. a brain tumour. At the end of this century Gowers attributed these findings to a raised resistance in the sensory and motor nerve cells in the brain that correspond with the limb involved. This would in turn arrest the spread of the discharge. Gowers[6] also reported several other ways by which sensory stimulation could prevent seizures from spreading e.g. pinching of the skin and inhalation of ammonia. Almost a hundred years later Rajna and Lona[7] demonstrated that afferent sensory stimuli can abort epileptic paroxysms in humans.

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## ANATOMICAL BASIS

The left vagus nerve is a mixed cranial nerve that consists of ∼80% afferent fibres originating from the heart, aorta, lungs and gastrointestinal tract and of ∼20% efferent fibres that provide parasympathetic innervation of these structures and also innervate the voluntary striated muscles of the larynx and the pharynx[8]. Somata of the efferent fibres are located in the dorsal motor nucleus and nucleus ambiguus, respectively. Afferent fibres have their origin in the nodose ganglion and primarily project to the nucleus of the solitary tract. The nucleus of the solitary tract (NTS) has widespread projections to numerous areas in the forebrain as well as the brainstem including important areas for epileptogenesis such as the amygdala and the thalamus. There are direct neural projections into the raphe nucleus, which is the major source of serotonergic neurons and indirect projections to the locus coeruleus and A5 nuclei that contain noradrenergic neurons. Finally, there are numerous diffuse cortical connections. The diffuse pathways of the vagus nerve mediate important visceral reflexes such as coughing, vomiting, swallowing, control of blood pressure and heart rate. Heart rate is mostly influenced by the right vagus nerve that has dense projections primarily to the atria of the heart[9].

## MECHANISMS OF ACTION

Early ***animal experiments*** investigated the effect of stimulation of the cervical vagus nerve on the *EEG*. Depending on the level of anaesthesia and the stimulus parameters used, vagus nerve stimulation (VNS) can induce EEG synchronization, EEG desynchronization, rapid eye movement and sleep or slow wave sleep[10,11]. Desynchronization results from high-intensity and high-frequency (>70 Hz) stimuli activating unmyelinated C-fibres. Lower intensity, high-frequency (>70 Hz) stimulation induces synchronization due to activation of myelinated A- and B-fibres. Desynchronization may also be caused by high-intensity, slower stimulation in the range of 20–50 Hz. VNS blocks interictal spike activity induced by strychnine applied to the cortex of the cat[10]. Zabara[12]. found that generalized seizures in dogs induced by pentylenetetrazol and strychnine were inhibited by VNS and he made an estimation about optimal stimulation parameters. These were found to be 20–30 Hz frequency, 3.5–7 mA output current and 0.2 milliseconds stimulus duration. Woodbury and Woodbury[13] established the anticonvulsant efficacy of VNS using frequencies above 4 Hz in rats after induction of seizures with pentylenetetrazol, mercaptoproprionate and maximal electroshock. Chronic VNS also reduced the frequency of recurrent spontaneous seizures in monkeys with alumina gel foci[14]. Using c-fos, a nuclear protein that is expressed in neurons as a result of high neuronal activity, Naritoku *et al.*[15] were the first to identify some key structures in the neuronal network between brainstem and forebrain that are activated during VNS. VNS induced severe staining in limbic structures such as the amygdala, a highly epileptogenic region that plays a role in the generalization of seizures. The habenula and posteromedian nucleus of the thalamus, structures implicated in seizure regulation, also showed intense c-fos immunoreactivity. Support for a role of monoamines in the mechanism of action of VNS was found through VNS induced c-fos activation in the locus coeruleus and A5 nuclei of the brainstem. Takaya *et al.*[16] showed that the antiseizure effect of VNS outlasts the duration of the stimulation train and repetition of stimuli increases VNS efficacy. Krahl *et al.*[17] performed bilateral lesioning of the locus coeruleus in rats that was shown to block the anticonvulsant effects of VNS by preventing VNS-induced norepinephrine release. Walker *et al.*[18] showed that an increase in $\gamma$-aminobutyric acid (GABA) or a decrease of glutamate transmission in the rat NTS reduces the severity of limbic seizures. VNS may therefore exert its antiseizure effect by inhibition of ascending outputs from the NTS that project via various anatomic connections to the forebrain. Krahl *et al.*[19] found strong evidence that vagal C-fibres are not responsible nor necessary for the seizure-suppressing effect of VNS. According to their experiments in awake and freely moving rats, activation of myelinated A- and B-fibres were shown to be responsible for seizure suppression. The efficacy and mode of action of VNS has mainly been studied in acute animal models for epilepsy. Fernandez-Guardiola *et al.*[20] performed VNS studies in electrically kindled cats, a model for chronic epilepsy. Their results showed that VNS delays the development of seizures induced by electrical kindling in the amygdala suggesting a possible preventative effect of VNS on epileptogenesis. These results were confirmed by Naritoku *et al.*[21] who evaluated the effects of VNS in electrically kindled rats. To date no studies in animal models with spontaneous primary generalized epilepsy have been published. Preliminary results from our group[22] at Ghent University Hospital who studied VNS in genetic absence epilepsy rats from Strasbourg (GAERS), suggest that short-term VNS does not reduce frequency or duration of absence seizures.

The first ***experimental work in humans*** aimed to reproduce the *EEG* findings from animal experiments. VNS-induced suppression of *interictal* epileptic activity recorded by scalp EEG could not be demon-

strated[23]. In one patient *ictal* EEG activity was abruptly terminated by acute VNS. In another patient bilateral rhythmical delta activity during an aura was also interrupted by acute VNS. In three other patients acute VNS, delivered well into an ongoing seizure, did not have any influence on the EEG or behavioural symptoms. Using fast Fourier EEG analysis, no changes of normal background EEG during wakefulness, sleep or anaesthesia were found. Acute or chronic VNS does not have any influence on the different diagnostic EPs (visual, auditory brainstem, auditory 40 Hz and long-latency cognitive EPs)[24]. Naritoku *et al.*[25] performed brainstem auditory *evoked potentials* (BAEP) and somatosensory evoked potentials (SSEP) to determine if chronic VNS results in electrophysiologically measurable changes. There was no influence on BAEP. There was a significant increase in the interval between cervicomedullary and thalamocortical potentials (N13–N20 interval) when three VNS patients were compared after 1 month of stimulation with three normal individuals and with baseline findings before VNS. Findings by Naritoku *et al.*[26] were confirmed in another study that showed delays in latencies of evoked responses induced by direct oesophagal stimulation in VNS treated patients. *Neurochemical* studies quantified amino-acid and neurotransmitter metabolite concentrations in CSF samples before and after VNS in order to clarify the hypothesis that VNS might act through the release of neurotransmitters and other compounds at the projection site of the vagus nerve[27, 28]. The first study revealed selective increases in 5-hydroxyindoleacetic acid and homovanillic acid, metabolites of serotonin and dopamine, respectively. Also a significant decrease of the levels of aspartate was found correlating with better seizure control. The second study revealed increased GABA and ethanolamine levels, mainly in responders. While serotoninergic as well as dopaminergic systems have been found to have anticonvulsant effects in animal and human studies of various types of epilepsy, it remains to be clarified whether these findings are epiphenomena or findings directly related to VNS. Finally the effect of VNS on human CNS structures has been studied through *cerebral blood flow (CBF) studies*. Various changes in supratentorial and cerebellar CBF caused by acute and chronic VNS have been reported. Garnett *et al.*[29] found ipsilateral activation in the thalamus and cingulate gyrus in five patients. A study by Ko *et al.*[30] in three patients reported increased CBF in the left posterior cerebellum and putamen and in the right medial temporal gyrus and thalamus. The main conclusion was that VNS induces measurable CBF changes in anatomic structures that are part of the diffuse vagus nerve pathways. Occurrence of (subclinical) seizures during scanning and previous resective surgery in these early studies may have influenced the results and may account for discrepancies in the reported findings. Ko[31] extended his study and finally examined nine individuals in whom changes in CBF were correlated with seizure control. A reduction in seizure frequency best correlated with decreased CBF in the right fusiform gyrus. VNS was also shown to exert an effect on CBF longer than the duration of the stimulation train. The first PET study of acute VNS showed diffuse CBF changes[32]. Acute CBF changes were correlated with seizure control after 3 months of VNS (three responders vs. 11 non-responders). Bilateral thalamic hyperperfusion correlated most significantly with a decrease in seizure frequency suggesting that alterations in thalamic activity may contribute to antiseizure effects of VNS. Repeated PET studies in the same patients after 3 months showed that decreased CBF in bilateral hippocampi, amygdala and cingulate gyrus and increased bilateral insular CBF that was found during acute VNS was no longer present[33]. Our group[34] performed an acute $^{99m}$Technetium SPECT activation study in 11 patients, receiving an initial stimulation train (*output*: 0.25–0.50 mA, *frequency*: 30 Hz, *pulse width*: 500 $\mu$seconds, *on time*: 30 seconds), that revealed ipsilateral thalamic hypoperfusion as the most significant finding. No significant CBF increases were found. In a follow-up study 23 patients underwent an acute activation paradigm and a subgroup of 10 patients also underwent a SPECT activation study after 6 months of chronic VNS. CBF changes were compared with clinical outcome[35]. Chronic VNS (as compared to baseline CBF before stimulation) resulted in decreased CBF in bilateral thalami and the left caudate head. During the activation paradigm in a chronic situation in which the generator was activated with an additional 0.25 mA during 30 seconds a significant left thalamic activation was found. An acute PET study by the same group during the first stimulation train (0.25–0.50 mA, 30 Hz, 500 $\mu$seconds, 30 seconds) in six patients[36] showed significantly increased CBF in the right thalamus and somatosensory cortex and left inferior cerebellum. Significantly decreased CBF was found in the left fusiform gyrus and in bilateral dorsolateral parietal cortex. In a recent study with eight patients Ring *et al.*[37] found a bilateral thalamic perfusion decrease after chronic intermittent stimulation.

## NCP DEVICE AND SURGICAL PROCEDURE[38]

In man, stimulation of the vagus nerve is facilitated by implantation of the Neurocybernetic Prosthesis (NCP$^{TM}$) System (Cyberonics Inc, Houston, Texas), which comprises a pulse generator and bipolar helical

lead with an integral tether. The surgical procedure requires two incisions. The first, for the pulse generator, is approximately 8 cm wide and 2 cm beneath the left clavicle and the other approximately 10 cm wide at the anterior border of the left sternocleidomastoid muscle. The operative procedure is usually performed under general anaesthesia with the patient remaining in the hospital overnight. Some centres are, however, turning to regional anaesthesia and day care surgery. Programming is facilitated with a radio frequency telemetry wand connected to an IBM compatible computer loaded with the NCP$^{TM}$ software. The programmable parameters, together with their ranges, are shown in Table 1. Stimulation can be initiated immediately after the surgical procedure when the patient is still under anaesthesia or after the patient has fully recovered from the surgery, typically 1–2 weeks later. In either case, the output current is subsequently increased according to patient tolerance. The patient may also be provided with a magnet. The magnet allows additional stimulation to be commanded by the patient or carer in case of an aura or a seizure. Additional stimulation is facilitated by passing the magnet over the pulse generator for 1–2 seconds. The magnet may also be used to inhibit stimulation by keeping it over the generator. The system can be safely removed by explanting the generator and lead[39]. Since the first human implant an estimated 10 000 patients have been treated with VNS.

## CLINICAL TRIALS

### Clinical efficacy and side effects

Five (E01–E05) acute-phase clinical studies involving the NCP$^{TM}$ system have been conducted in a total population of 454 patients. The purpose of the studies was to determine whether adjunctive use of electrical stimulation of the left vagus nerve could reduce seizure frequency in patients with refractory epilepsy[40–43]. The E01 and E02 studies were two pilot studies that enrolled 15 patients with refractory partial epilepsy of whom 14 received stimulation. In one patient the NCP device was explanted because of a surgical complication that resulted in unilateral vocal cord paralysis which resolved 9 months later. The degree of response ranged from no improvement to complete cessation of seizures with a mean reduction of 46.6%. In none of the patients did the seizure disorder appear to have exacerbated by VNS. Of 14 patients, five reported a reduction in seizure frequency of at least 50%. None of the patients reported transient or permanent serious side effects. The most common side effects were noted only during actual stimulation of the nerve and consisted of hoarseness and local neck/throat paraesthesias. These effects became milder after a few months of stimulation. No cardiac or gastrointestinal negative effects were observed on ECG monitoring and measurements of gastric acid output.

The E03 (114 patients) and E05 (196 patients) studies were both randomized, blinded, active control trials in which patients with refractory partial epilepsy were randomly assigned into two treatment groups. Patients assigned to treatment with *'high'* stimulation parameters (output current: 0.25–3 mA; frequency: 20–50 Hz; pulse width: 500 $\mu$seconds; on-time: 30–90 seconds; off- time: 5–10 minutes) were believed to receive therapeutic treatment. Treatment with *'low'* stimulation parameters (output current: 0.25–2.75 mA; frequency: 1– 2 Hz; pulse width: 130 $\mu$seconds; on-time: 30 seconds; off-time: 60–180 minutes) was considered to be non-therapeutic. The primary efficacy endpoint was the percentage reduction in seizure rate measured over a period of 12 weeks. Adverse events were assessed at each patient visit. In the high stimulation groups there was a mean reduction in seizure frequency of 24 and 28% in the E03 and E05 studies, respectively. This is a statistically significant decrease in seizure frequency when compared with baseline seizure frequency and seizure frequency reduction in the low stimulation groups (6 and 15%, respectively). The most common treatment related adverse events were attributable to vagal innervation of the larynx during current 'on' periods and consisted of voice alteration, coughing, throat paraesthesias and discomfort and dyspnea. Treatment was well tolerated; 97% of patients remained in the long-term follow-up phase of the study. Surgical-related complications included left vocal cord paralysis in two patients, lower facial muscle paresis in two patients, fluid accumulation over the generator requiring aspiration in one patient. All these complications resolved. Infection around the device occurred in three patients. VNS had no effect on concurrent AED serum levels or on body chemistry. Rigorous blinded collection of autonomic measures revealed no effect on weight, serum gastrin, cardiac or pulmonary function tests. Administered at levels that do not exceed comfort electrical stimulation of the left vagus nerve has no demonstrable effects on visceral functions. The E04 study was an open study in which 116 patients with all types of epilepsy and patients under 12 years of age were stimulated. In this study 29% of the implanted patients had a seizure reduction of more than 50%.

### Long-term efficacy and safety

Long-term data (>3 months) were collected on all available E01–E04 study patients. These long-

Table 1: Stimulation parameters available with the NCP™ system.

| Parameter | Units | Range | Typical parameter value |
|---|---|---|---|
| Output current | Milliamperes (mA) | 0–3.5 mA | 1.25 mA |
| Signal frequency | Hertz (Hz) | 1–143 Hz | 30 Hz |
| Pulse width | Microseconds ($\mu$s) | 130–1000 $\mu$s | 500 $\mu$s |
| Signal on-time | Seconds (s) | 7 s (rapid cycle)–270 s | 30 |
| Signal off-time | Seconds–minutes (s, min) | 14 s (rapid cycle)–180 min | 5 min |
| Lead impedance | Kiloohms (Kohms) | <1–7 Kohms | 3–4 Kohms |

term follow-up data are uncontrolled because they come from an open-label protocol in which both the AED medications and NCP device settings were allowed to be changed. Patients initially randomized to low stimulation parameters were changed to high stimulation parameters. George *et al.*[44] reported 18-months efficacy analysis in 50 patients exiting the E03 study and Salinsky *et al.*[45] reported efficacy data in 100 of 114 patients from the E03 study that were treated for 1 year. Results indicated that VNS remains as effective over time and a trend towards improved seizure control with longer use of VNS was observed. Response during the first 3 months of treatment is predictive of long-term response. Chronic side effects were identical to those observed during the randomized trials and consisted mainly of mild hoarseness during stimulus delivery. Several other reports on long-term treatment with VNS confirm these findings[46,47]. In our own study[47] up to 10% of patients became seizure free. Ben-Menachem[48] recently published data on 64 patients with follow-up of up to 5 years. The study included patients with partial seizures, Lennox–Gastaut syndrome (LGS) and primary generalized seizures (PGS). Forty-four percent of patients experienced a large reduction in seizure frequency and severity over long periods of time. VNS seems equally efficacious for LGS and PGS but results from larger patient groups are necessary. Two patients became pregnant and have given birth to healthy babies.

Bradycardia and asystole have been reported as a rare complication during intraoperative testing of the NCP™ device, probably due to stimulation of the cervical cardiac branches of the vagus nerve either directly or by collateral current spread[49]. Patients treated with VNS have a comparable rate of sudden unexpected unexplained death (SUDEP) compared to patients treated with novel antiepileptic drugs. The SUDEP rate became lower during a 2-year follow-up[50].

Little is known about the cognitive effects of VNS. All studies agree that VNS lacks the sometimes considerable cognitive side effects of many antiepileptic drugs. Measures of neuropsychological outcome in different patient populations showed a moderate improvement in mental functioning, mood and behaviour[51–53]. Specific enhancement of recognition memory was demonstrated following VNS by Clark *et al.*[54].

VNS is currently being investigated for use in major depression. The first human trials showed significant improvements of several mood scores during short-time follow-up[55,56]. VNS has also been shown to suppress experimentally induced pain by a central inhibitory effect[57].

### Experience in children and elderly

Experience with VNS in children is less extensive than in adults but results seem promising. Two studies report seizure frequency reductions of >60% in 80% of children and >50% in 38% of children[58]. The most recent and largest study in 60 children with mean age of 15 years reported a reduction in seizure frequency similar to that in adults[59]. Median reduction of seizure frequency was 44%. A gradual increase in efficacy up to 18 months post-operatively was observed. The predominant seizure type in this study was complex partial (57%) followed by generalized tonic–clonic seizures (27%). No particular seizure or epilepsy type appeared particularly sensitive or resistant to VNS. Adverse events during stimulation included fever, coughing, colds and voice alteration. No patients dropped out and side effects subsided over time.

A single review of 45 patients older than 50, who participated in the E03, E04 and E05 trials, showed that more than 60% of patients had a >50% seizure reduction after a follow-up of 1 year. Side effects were mild and transient and quality of life scores improved significantly[60].

## COST–BENEFIT CONSIDERATIONS

VNS is a costly treatment. Few cost–benefit data are available. A recent study showed that there is a significant decrease in epilepsy related direct medical costs after implantation with the vagus nerve stimulator. This decrease is mainly due to an important decrease in the number of hospital admission days

after implantation. It is estimated that the cost of the device can be paid back by savings in epilepsy-related direct medical costs after 2.5 years. Battery life now exceeds 4 years[61]. The current generator model has an estimated battery life of 8 years. In a comparative study of conservative treatment, resective epilepsy surgery and VNS, VNS was demonstrated to have a favourable cost-efficacy in patients who were unsuitable candidates for resective surgery[62].

## CURRENT PRACTICAL MANAGEMENT

In many epilepsy centres VNS is a routinely performed treatment for patients who are unsuitable candidates for epilepsy surgery or who have had insufficient benefit from such a treatment. When patients with refractory epilepsy are referred to our epilepsy centre they are initially included in a pre-surgical evaluation protocol including video-EEG monitoring, optimum magnetic resonance imaging (MRI), PET and neuropsychological examination. Results of these examinations are discussed in the epilepsy surgery meeting by a multidisciplinary team. Patients who are considered unsuitable candidates for resective surgery can be included in phase-III drug trials with new AEDs or they can be offered implantation with a vagus nerve stimulator. Absolute contraindications for implantation of a vagus nerve stimulator are limited to previous left or bilateral cervical vagotomy. A stimulator will not be implanted when there is evidence of progressive intracerebral disease. This does not necessarily include patients with progressive myoclonic epilepsy, tuberous sclerosis, hypothalamic hamartoma, etc.[63–65]. Other conditions that need special attention are cardiac arrhythmias, respiratory diseases like asthma and pre-existing hoarseness, gastric ulcers, vasovagal syncope and coexisting neurological diseases other than epilepsy. Patients who were evaluated for epilepsy surgery several years ago when treatment with a vagus nerve stimulator was not yet routinely available are rediscussed on the epilepsy surgery meeting and will be reevaluated with current optimum MRI or repeated pre-surgical investigations (e.g. video-EEG monitoring) when updating of the available clinical data set seems necessary.

Patients are extensively informed about the efficacy, side effects, implantation procedure and ramping up procedure. After informed consent is obtained they are admitted into a neurosurgical unit for 48 hours. The surgical procedure is performed under general anaesthesia and lasts about 1 hour. Patients leave the hospital with the stimulator unprogrammed. Two to four weeks after the operation the vagus nerve stimulator is programmed to continuous intermittent stimulation during a clinic visit, starting by an initial 0.25–0.50 mA output current depending on individual patient tolerance. Every 2–4 weeks the stimulation output current is gradually ramped up with 0.25–0.50 mA until clinical efficacy or patient tolerance is reached. When patients are used to the electrical stimulation they are provided with the magnet. At every clinic visit seizure frequency and side effects are assessed. AEDs remain unchanged during ramping up. Tapering of AEDs may be considered when seizure freedom is achieved. After ramping up patients are seen in follow-up every 3–4 months. The presence of the NCP$^{TM}$ is not considered a contraindication for performing an MRI, provided that the generator be turned of during the imaging sequences, that lengthy MRI sessions be avoided and only a transmit and receive type head coil be used. If the pulse generator is implanted with the electrode inputs parallel to the long axis of the body, it need not be deactivated when an MRI scan is performed[66].

## CONCLUSION

VNS is an efficacious but palliative treatment for patients with refractory epilepsy. The current consensus on efficacy is that 1/3 of patients have a considerable improvement in seizure control with a reduction in seizure frequency of at least 50%, 1/3 of patients experience a worthwhile reduction of seizure frequency between 30 and 50%. In the remaining 1/3 of the patients there is little or no effect. Efficacy has a tendency to improve with longer duration of treatment up to 18 months post-operatively. There is only limited information on patients becoming seizure free. VNS seems equally efficient for children. Analysis of larger patient groups and insight in the mode of action may help to identify patients with epileptic seizures or syndromes that respond better to VNS and guide the search for optimal stimulation parameters. Further improvement of clinical efficacy of VNS and development of other neurostimulation strategies for epilepsy may result from this. In the near future, VNS is likely to be used as a treatment for other conditions such as depression and pain.

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