Vagal nerve stimulation – a 15-year survey of an established treatment modality in epilepsy surgery

K. Vonck, V. De Herdt, and P. Boon

Department of Neurology, Ghent University Hospital, Gent, Belgium

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Contents

Abstract

Neurostimulation is an emerging treatment for neurological diseases. Electrical stimulation of the tenth cranial nerve or vagus nerve stimulation (VNS) has

become a valuable option in the therapeutic armamentarium for patients with refractory epilepsy. It is indicated in patients with refractory epilepsy who are unsuitable candidates for epilepsy surgery or who have had insufficient benefit from such a treatment. Vagus nerve stimulation reduces seizure frequency with >50% in 1/3 of patients and has a mild side effects profile.

Research to elucidate the mechanism of action of vagus nerve stimulation has shown that effective stimulation in humans is primarily mediated by afferent vagal A- and B-fibers. Crucial brainstem and intracranial structures include the locus coeruleus, the nucleus of the solitary tract, the thalamus and limbic structures. Neurotransmitters playing a role may involve the major inhibitory neurotransmitter GABA but also serotoninergic and adrenergic systems. This manuscript reviews the clinical studies investigating efficacy and side effects in patients and the experimental studies aiming to elucidate the mechanims of action.

Introduction

Epilepsy affects 0.5–1% of the population and is therefore the second most common chronic neurological disease following cerebrovascular disorders [1]. More than 30% of all epilepsy patients have uncontrolled seizures or unacceptable medication-related side effects despite adequate pharmacological treatment [2]. In these patients a thorough diagnostic and therapeutic work-up in a specialised epilepsy center is warranted. Few therapeutic options are available for patients with refractory epilepsy. Epilepsy surgery aims at the removal of the ictal onset zone. It is an invasive treatment option resulting in seizure freedom in up to 85% of the patients depending on the localization of the seizure focus [3]. Due to strict criteria during the presurgical evaluation protocol a large number of patients are considered unsuitable candidates [4]. In these patients a circumscribed, unifocal ictal onset cannot be identified or the ictal onset zone is localized in functional brain tissue as demonstrated by the Wada-test and functional MRI [5].

The inability to adequately treat all patients with refractory epilepsy provides a continuous impetus to investigate novel forms of treatment. Neurostimulation is an emerging treatment for neurological diseases. Electrical pulses are administered directly to or in the neighbourhood of nervous tissue in order to manipulate a pathological substrate and to achieve a symptomatic or even curative therapeutic effect. Different types of neurostimulation exist depending on the part of the nervous system that is being affected and the way this stimulation is being administered.

Electrical stimulation of the tenth cranial nerve or vagus nerve stimulation (VNS) is an extracranial form of neurostimulation that was developed in the

eighties. In the past decade it has become a valuable option in the therapeutic armamentarium for patients with refractory epilepsy and it is currently routinely available in epilepsy centers worldwide. Through an implanted device and electrode, electrical pulses are administered to the afferent fibers of the left vagus nerve in the neck. It is indicated in patients with refractory epilepsy who are unsuitable candidates for epilepsy surgery or who have had insufficient benefit from such a treatment [6].

The first vagus nerve stimulator was implanted in humans in 1989. 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 was described by the ancient Greek author 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 and Brown-Séquard showed that ligatures are equally efficacious in arresting seizures caused by organic brain disease e.g. a brain tumor [7]. 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 also reported several other ways by which sensory stimulation could prevent seizures from spreading e.g. pinching of the skin and inhalation of ammonia [8]. Almost a hundred years later Rajna and Lona demonstrated that afferent sensory stimuli can abort epileptic paroxysms in humans [9].

The vagus nerve is a mixed cranial nerve that consists of ∼80% afferent fibers originating from the heart, aorta, lungs and gastrointestinal tract and of ∼20% efferent fibers that provide parasympathetic innervation of these structures and also innervate the voluntary striated muscles of the larynx and the pharynx [10–12]. Somata of the efferent fibers are located in the dorsal motor nucleus and nucleus ambiguus respectively. Afferent fibers have their origin in the nodose ganglion and primarily project to the nucleus of the solitary tract (NTS). At the cervical level the vagus nerve mainly consists of small diameter unmyelinated C-fibers (65–80%) and of a smaller portion of intermediate-diameter myelinated B-fibers and large-diameter myelinated A-fibers. The nucleus of the solitary tract has widespread projections to numerous areas in the forebrain as well as the brain stem 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 noradrenegic 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 [13]. Relatively few specific functions of the vagus nerve have been well characterised. Figure 1 depictures a schematic
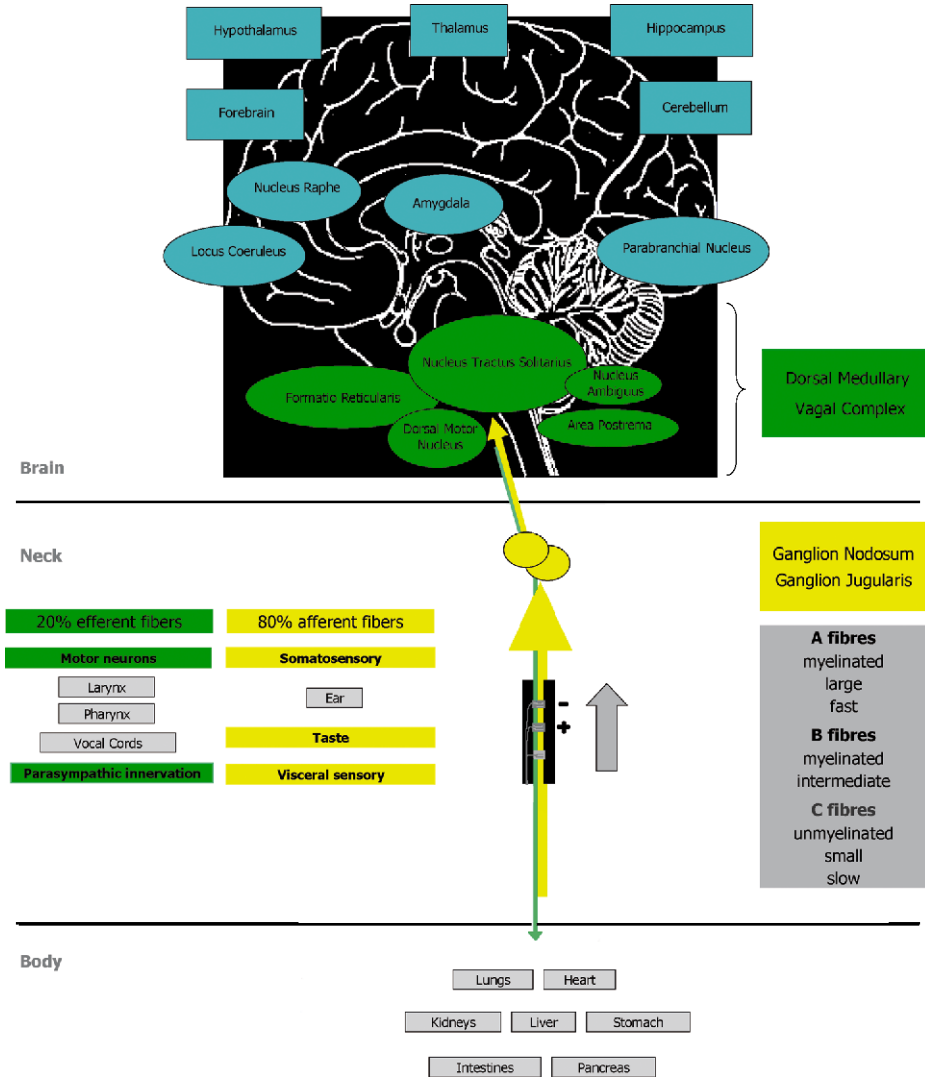
Fig. 1. Schematic drawing of the vagus nerve anatomy. Structures of importance for the mechanism of action in the brain and brain stem: locus coeruleus [23], thalamus [21], temporal lobe structures [21, 31]. Vagus nerve stimulation aims at inducing action potentials within the different types of fibers that constitute the nerve at the cervical level. Unidirectional stimulation of afferent vagal fibers is preferred as epilepsy is considered a disease with cortical origin and efferent stimulation may cause side effects of innervated internal organs

drawing of the vagus nerve anatomy and structures demonstrated to play a role in the mechanism of action.

The vagus nerve is often considered protective, defensive, relaxing. This primary function is exemplified by the lateral line system in fish, the early precedent of the autonomic nervous system. The control of homeostatic functions by the central nervous system in these earlier life forms was limited to the escape and the avoidance of perturbing stimuli or suboptimal conditions. Its complex anatomical distribution has earned the vagus nerve its name, as vagus is the Latin word for wanderer. These two facts together inspired Andrews and Lawes to suggest the name "great wandering protector" [14].

Mechanism of action

Since the first human implant of the VNS Therapy^{TM} device in 1989, over 50,000 patients have been treated with VNS worldwide. As for many antiepileptic treatments, clinical application of VNS preceded the elucidation of its mechanism of action (MOA). Following a limited number of animal experiments in dogs and monkeys, investigating safety and efficacy, the first human trial was performed [15]. The basic hypothesis on the MOA was based on the knowledge that the tenth cranial nerve afferents have numerous projections within the central nervous system and that in this way action potentials generated in vagal afferents have the potential to affect the entire organism [16]. To date the precise mechanism of action of VNS and how it suppresses seizures remains to be elucidated. Crucial questions with regards to the MOA of VNS occur at different levels. Vagus nerve stimulation aims at inducing action potentials within the different types of fibers that constitute the nerve at the cervical level. The question remains, what fibers are responsible and/or necessary for its seizure-suppressing effect. Unidirectional stimulation, activating afferent vagal fibers, is preferred as epilepsy is considered a disease with cortical origin and efferent stimulation may cause side effects. The next step is to identify central nervous system structures located on the anatomical pathways from the cervical part of the vagus nerve up to the cortex, that play a functional role in the MOA of VNS. These could be central gateway or pacemaker function structures such as the thalamus or more specific targets involved in the pathophysiology of epilepsy such as the limbic system or a combination of both. Another issue concerns the identification of the potential involvement of specific neurotransmitters. The intracranial effect of VNS may be based on local or regional GABA increases or glutamate and aspartate decreases or may involve other neurotransmitters that have been shown in the past to have a seizure threshold regulating role such as serotonine and norepinephrine [17]. When considering the efficacy of a given treatment in epilepsy, a certain hierarchical profile of the treatment can be distinguished. A treatment can have

pure anti-seizure effects meaning that it can abort seizures. To confirm such an effect the treatment is most often administered during an animal experiment in which the animals are injected with a proconvulsant compound followed by the administration of the treatment under investigation. A treatment can have a true preventative or so-called anti-epileptic effect. Antiepileptic efficacy implicates that a treatment can prevent seizures, as the main characteristic of the disease namely the unexpected recurrence of seizures is prevented from happening. A treatment can also have an antiepileptogenic effect. This implies that the treatment reverses the development of a pathological process that may have evolved over a long period of time. Such a treatment is clearly protective and may even be used for other neuroprotective purposes. Research directed towards investigating the antiseizure, antiepileptic and potential antiepileptogenic properties of VNS as well as towards the identification of involved fibers, intracranial structures and neurotransmitter systems has been performed. Animal experiments and research in humans treated with VNS have comprised electrophysiological studies (EEG, EMG, EP), functional anatomic brain imaging studies (PET, SPECT, fMRI, c-fos, densitometry), neuropsychological and behavioural studies. Also from the extensive clinical experience with VNS interesting clues concerning the MOA of VNS have arisen. More recently the role of the vagus nerve in the immune system has been investigated. From the extensive body of research on the MOA, it has become conceivable that effective stimulation in humans is primarily mediated by afferent vagal A- and B-fibers [18, 19]. Unilateral stimulation influences both cerebral hemispheres, as shown in several functional imaging studies [20, 21]. Crucial brainstem and intracranial structures have been identified and include the locus coeruleus, the nucleus of the solitary tract, the thalamus and limbic structures [22–25]. Neurotransmitters playing a role may involve the major inhibitory neurotransmitter GABA but also serotoninergic and adrenergic systems [26, 27]. More recently, Neese *et al.* found that VNS following experimental brain injury in rats protects cortical GABAergic cells from death [28]. A SPECT study in humans before and after 1 year of VNS showed a normalisation of GABAA receptor density in the individuals with a clear therapeutic response to VNS [29]. Follesa *et al.* showed an increase of norepinephrine concentration in the prefrontal cortex of the rat brain after acute VNS [30]. An increased norepinephrine concentration after VNS has also been measured in the hippocampus [31] and the amygdala [32, 33]. Currently, VNS as a neuroimmunomodulatory treatment is being explored. As the vagus nerve plays a critical role in the signalisation and modulation of inflammatory processes, the so-called anti-inflammatory pathway, this could represent a new modality in the MOA of VNS for epilepsy [33, 34].

Early animal experiments in acute seizure models suggest an anti-seizure effect of VNS. McLachlan found that applying VNS at the beginning of a PTZ-

induced seizure significantly shortened the seizure [35]. Woodbury described the beneficial effect of VNS in preventing or reducing PTZ-induced clonic seizures and electrically-induced tonic-clonic seizures in rats [36]. Zabara found that VNS interrupts or abolishes motor seizures in canines induced by strychnine [37]. In our own group, VNS significantly increased the seizure threshold for focal motor seizures in the cortical stimulation model [38]. Also in the human literature, evidence exists that VNS may exert an acute abortive effect. The magnet feature allows a patient to terminate an upcoming seizure [39]. Also, a few case reports describe the use of VNS for refractory SE in pediatric and adult patients [40, 41]. A recent study investigated the effects of acute VNS on cortical excitability by using transcranial magnetic stimulation (TMS) [42]. However, in the clinical trials with VNS, many patients did not regularly self-trigger the device at the time of a seizure and still showed good response to VNS. Moreover, VNS is administered in an intermittent way and it appears that seizures occurring during the VNS off-time are also affected. This intermittent way of stimulation is insufficient to explain the reduction of seizures on the basis of abortive effects alone and suggests a true preventative or so-called antiepileptic effect of VNS. The fact that VNS influences seizures at a time when stimulation is in the off-mode has also been shown in many animal and human experiments. Already in 1985, Zabara reports that seizure control was extended well beyond the end of the stimulation period. Stimulation for one minute could produce seizure suppression for 5 min [37, 43]. Naritoku *et al.* showed that VNS pretreatment during 1 and 60 min, prior to administration of the seizure triggering stimulation, significantly reduced the duration of behavioural seizures and the duration of afterdischarges in amygdala kindled rats [44]. In a study of Takaya *et al.* VNS was discontinued before induction of PTZ-seizures that were significantly shortened in duration. Moreover, repetition of stimuli increased VNS efficacy suggesting that efficacy of intermittent stimulation improves with long-term use [45]. Zagon *et al.* found that VNS-induced slow hyperpolarization in the parietal cortex of the rat outlasted a 20 s VNS train with 15 s [19]. McLachlan *et al.* found that interictal spike frequency was significantly decreased or abolished after 20 s of VNS in rats for a variable duration, usually around 60 s to 3 min after stimulation discontinuation [46]. Recent data in human EEG studies show a decrease in interictal epileptiform discharges, both in an acute form and after long-term follow-up [47, 48]. The fact that seizures reoccur after end of battery life has been reached is a strong argument against VNS having an antiepileptogenic effect. However, as progress in the development of more relevant animal models for epilepsy has been made, the antiepileptogenic potential of neurostimulation in general is being fully explored and some promising results have been reported e.g. in the kindling model [44, 49]. In human literature, one case report described long-lasting seizure control after explantation of the VNS device [50]. The basis for

Table 1. *Controlled clinical trials*

Reference	Type of study	Nr. of patients	Efficacy	Stimulation related side-effects	Non-stimulation related side-effects	Follow-up (months)
Holder LK et al. (1992) Treatment of refractory partial seizures: preliminary results of a controlled study. Pacing and Clinical Electrophyisology 15(10): 1557–71	preliminary results EO3-study randomized double blind active control	37	HIGH stimulation group: 33% mean SF reduction LOW stimulation group: 8.4% mean SF reduction			3
Ben-Menachem E et al. (1994) Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. Epilepsia 35(3): 616–26	EO3-study randomized double blind active control multicenter	67	HIGH stimulation group (n = 31): 31% mean SF reduction LOW stimulation group (n = 36): 11% mean SF reduction			3
Ramsay RE et al. (1994) Vagus nerve stimulation for treatment of partial seizures 2. Safety, side-effects and tolerability. Epilepsia 35: 627–36	EO3-study randomized double blind active control multicenter	67		Hoarseness (36%), Coughing (14%) Throat pain (13%)		3

Reference	Study design	n	Efficacy	Side effects		
The Vagus Nerve Stimulation Study Group (1995) A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology 45: 224–30	EO3-study randomized double blind active control multicenter	114	HIGH stimulation group (n = 54): 25% mean SF reduction LOW stimulation group (n = 60): 6% mean SF reduction	Hoarseness (37%) Throat pain (11%) Coughing (7%)	Left vocal cord paralysis due to device malfunctioning (1/31)	3
Handforth A et al. (1998) Vagus nerve stimulation therapy for partial onset seizures. A randomized, active control trial. Neurology 51: 48–55	EO5-study randomized double blind active control multicenter	196	HIGH stimulation group (n = 94): 28% mean SF reduction LOW stimulation group (n = 102): 15% mean SF reduction	Voice alteration (66%) Cough (45%) Pharyngitis (35%) Pain (28%) Dyspnea (25%)	Left vocal cord paralysis (2), lower facial muscle paresis (2), infection (3)	3

the combined acute and more chronic effects of VNS most likely involves recruitment of different neuronal pathways and networks. The more chronic effects are thought to be a reflection of modulatory changes in subcortical site-specific synapses with the potential to influence larger cortical areas. In the complex human brain these neuromodulatory processes require time to build up. Once installed, certain antiepileptic neural networks may be more easily recruited, e.g. by changing stimulation parameters that may then be titrated to the individual need of the patient. This raises hope for potential anti-epilepto-genic properties of VNS using long-term optimized stimulation parameters that may affect and potentially reverse pathological processes that have been installed over a long period of time. However, from a clinical point of view, up till now VNS cannot be considered a curative treatment.

Clinical efficacy and safety

Randomised controlled trials (Table 1)

The first descriptions of the implantable VNS Therapy™ system for electrical stimulation of the vagus nerve in humans appeared in the literature in the early ninetees [51, 52]. At the same time initial results from single-blinded pilot clinical trials (phase-1 trials EO1 and EO2) in a small group of patients with refractory complex partial seizures who were implanted since November 1988 in three epilepsy centers in the U.S.A. were reported [15, 53, 54]. In 9/14 patients treated for 3–22 months a reduction in seizure frequency of at least 50% was observed. One of the patients was seizure-free for more than 7 months. Some patients reported less severe seizures with briefer ictal and postictal periods. Complex partial seizures, simple partial seizures as well as secondary generalized seizures were affected. It was noticed that a reduction in frequency, duration and intensity of seizures lagged 4–8 weeks after the initiation of treatment [15]. In 1993, Uthman *et al.* reported on the long-term results from the EO1 and EO2 study [55]. Fourteen patients had now been treated for 14–35 months. There was a mean reduction in seizure frequency of 46%. Five patients had a seizure reduction of at least 50%, of whom 2 experienced long-term seizure freedom. In none of the patients VNS induced seizure exacerbation. It appeared that three types of responses to vagal stimulation occurred: rapid-sustained, gradual and non-response. In the meantime, two prospective multicenter (n = 17) double-blind randomised studies (EO3 and EO5) were started [56, 57]. In these two studies patients over the age of 12 with partial seizures were randomised to a HIGH or LOW stimulation paradigm. The parameters in the HIGH stimulation group (output: gradual increase up to 3.5 mA, 30 Hz, 500 μs, 30 s on, 5 min off) were those believed to be efficacious based on animal data and the initial human pilot studies. Because patients can sense stimulation, the LOW stimulation parameters (output: single increase to

Table 2. *Open long-term prospective clinical trials*

Reference	Type of study	Epilepsy type	Outcome measures	Efficacy at max. FU	Nr. of patients	FU (months)
Holder L et al. (1993) J Epilepsy 6: 206–14	open extension EO3	partial	efficacy safety and side-effects		37	18
George R et al. (1994) Epilepsia 35(3): 637–43	open extension EO3	partial	efficacy safety and side-effects	Mean SF reduction 38–52%	67	18
Salinsky MC et al. (1996) Arch Neurol 53: 1176–80	open extension EO3	partial	efficacy	Mean SF reduction 32%	100	12
Morris GL, Mueller WM. (1999) Neurology 53: 1731–35	open extension EO1–EO5	partial generalized seizures	efficacy safety and side-effects medication treatment	Mean SF reduction 44%	440	36
Ben-Menachem E et al. (1999) Neurology 52: 1265–67	open long-term	partial idiopathic generalized symptomatic generalized	efficacy	Responder rate 44%	64	3–64
DeGiorgio CM et al. (2000) Epilepsia 41(9): 1195–200	open extension EO5	partial generalized seizures	efficacy	Mean SF reduction 45%	195	12–15
Chavel SM et al. (2003) Epilepsy and Beh 4: 302–09	open long-term	partial	efficacy quality of life, depression and anxiety	Responder rate 12m: 54% Responder rate 24m: 61%	30	12–24
Vonck K et al. (2004) J Clin Neurophysiol 21: 283–89	open long-term 2-center	partial idiopathic generalized symptomatic generalized	efficacy safety and side-effects	Mean SF reduction 55%	118	6–94
Hui Che Fai A et al. (2004) Chin Med J 117(1): 58–61	open long-term	partial symptomatic generalized	efficacy safety and side-effects	Mean SF reduction 40%	13	18

point of patient perception, no further increase, 1 Hz, 130 µs, 30 s on, 3 h off) were chosen to provide some sensation to the patient in order to protect the blinding of the study. LOW stimulation parameters were believed to be less efficacious and the patients in this group represented an active control group. The results of EO3 in 114 patients were promising with a decrease in seizures of 24% in the HIGH stimulation group versus 6% in the LOW stimulation group after 3 months of treatment [56]. The number of patients was insufficient to achieve Food and Drug Administration (FDA) approval leading to the EO5 study in the U.S.A. including 196 patients. 94 patients in the HIGH stimulation group had a 28% decrease in seizure frequency versus 15% in patients in the LOW stimulation group [57].

Prospective clinical trials with long-term follow-up (Table 2)

The controlled EO3 and EO5 studies had their primary efficacy end-point after 12 weeks of VNS. Patients who ended the controlled trials were offered enrolment in a long-term (1–3 years of FU) prospective efficacy and safety study. Patients belonging to the LOW stimulation groups were crossed-over to HIGH stimulation parameters. In all published reports on these long-term results increased efficacy with longer treatment was found [58–62]. In these open extension trials the mean reduction in seizure frequency increased up to 35% at one year and up to 44% at two years of FU. After that improved seizure control reached a plateau [60]. In the following years, other large prospective clinical trials were conducted in different epilepsy centers worldwide. In Sweden, long-term follow-up in the largest patient series (n = 67) in one center not belonging to the sponsored clinical trials at that time, reported similar efficacy rates with a mean decrease in seizure frequency of 44% in patients treated up to 5 years [63]. A joint study of 2 epilepsy centers in Belgium and the USA included 118 patients with a minimum follow-up duration of 6 months. They found a mean reduction in monthly seizure frequency of 55% [64]. In China a mean seizure reduction of 40% was found in 13 patients after 18 months of VNS [65].

Prospective clinical trials in children

There are no controlled studies of VNS in children, but many epilepsy centers have reported safety and efficacy results in patients less than 18 years of age in a prospective way. All these studies report similar efficacy and safety profiles compared to findings in adults [66–69]. Rare adverse events, unique to this age group, included drooling and increased hyperactivity [70]. In children with severe mental retardation and pre-VNS dysphagia, swallowing problems might occur. Switching off the stimulator by applying the magnet over the device during meals may be helpful in such events [71]. In children with epileptic

encephalopathies efficacy may become evident only after >12 months of treatment [72]. A recent Korean multicenter study evaluated long-term efficacy in 28 children with intractable epilepsy. In half of the children there was a >50% seizure reduction after a FU of at least 12 months [73].

In our own prospective analysis of 118 patients, 13 children with a mean age of 12 years (range: 4–17 years) were included with similar efficacy rates and without specific side effects [74].

Clinical trials in specific patient groups

Generalized epilepsy

The clinical studies EO1, EO2, EO3 and EO5 included patients with partial epilepsy. This is a reflection of the fact that patients considered for treatment with VNS were initially evaluated for resective surgery, the preferred treatment for partial epilepsy, but turned out to be unsuitable surgical candidates. The open label longitudinal multicenter (n = 24) EO4 study also included patients with generalized epilepsy [75, 76]. In these patients overall seizure frequency reduction was 46%. Generalized tonic seizures responded significantly better than generalized tonic-clonic seizures. Quintana *et al.* [77], Michael *et al.* [78]. and Kostov *et al.* [79] described in a retrospective way that primary generalized seizures and generalized epilepsy syndromes responded equally well to VNS compared to partial epilepsy syndromes. A prospective study of Holmes *et al.* in 16 patients with generalized epilepsy syndromes and stable AED regimens showed an overall mean seizure frequency reduction of 43% after a follow-up of at least 12 months [80]. Ben-Menachem *et al.* included 9 patients with generalized seizures in a prospective long-term FU study. Especially the patients with absence epilepsy had a significant seizure reduction [63].

Status epilepticus

A few case-reports describing the use of VNS for refractory SE in pediatric and adult patients are available in the literature. Malik *et al.* reported on 3 children with pharmacoresistant SE who were successfully treated with VNS [40]. It was not specified whether the status was convulsive or nonconvulsive in these patients. Winston *et al.* reported a case of a 13-year old boy in whom VNS interrupted a convulsive SE immediately after stimulation was started [81]. Pathwardan *et al.* described a case of a 30-year old man with medically intractable seizures due to severe allergic reactions to multiple AEDs with subsequent evolvement into refractory SE. He underwent VNS treatment after nearly 9 days of barbiturate-induced coma. Stimulation was initated in the operating room. In the following days EEG revealed resolution of previously

observed periodic lateralized epileptiform discharges with the stimulator pro-
grammed at 1 mA and a duty cycle of 30 s on and 3 min off. The patient
became seizure-free [82]. Zimmerman *et al.* reported on 3 adult patients in
whom refractory non-convulsive SE due to AED withdrawal was treated with
VNS. After implantation of the device, stimulation output was rapidly in-
creased to 3 mA in the 3 patients. Time to termination of the SE was 3–5
days [83]. A case of our own group described the use of VNS in a 7-year old
child with a medically refractory non-convulsive SE [41].

Lennox-Gastaut syndrome

A few studies are available in literature specifically describing the use of VNS in
patients diagnosed with Lennox-Gastaut syndrome. One prospective study in
16 patients with Lennox-Gastaut (FU = 6 months) found that ¼ of patients
had a >50% reduction in seizure frequency which is comparable to the re-
sponse rates in the controlled studies, that included few patients with LGS [84].
Other prospective studies reported higher responder rates with a >50% seizure
frequency reduction in half of the patients (n = 13, FU = 6 months) [85], in
6/7 patients (FU = 6 months) [86] and in 7/9 patients (FU = 1–35 months)
[87]. A retrospective multicenter study that included 46 patients with LGS for
efficacy analysis, reported responder rates of 43% [88].
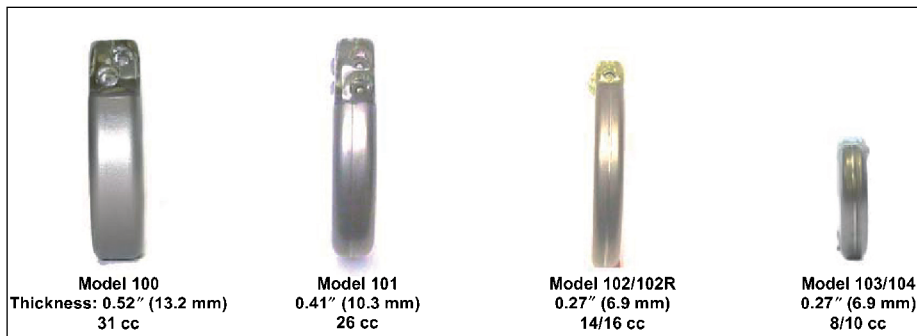
Other patient groups

There have been many reports on various other seizure types and syndromes
such as seizures in patients with hypothalamic hamartomas [89], tuberous
sclerosis [90], progressive myoclonic epilepsy [91, 92], Landau Kleffner syn-
drome [93], Asperger syndrome [94], epileptic encefalopathies [72] and syn-
dromes with developmental disability and mental retardation [95–97]. All these
studies reported good efficacy with regard to controlling seizures as well as
other disease-related symptoms such as cerebellar dysfunction, behavioural and
mood disturbances [72, 89, 91, 93, 96]. One study in children with infantile
spasms reported less favourable results with long-term benefit in only 2/10
patients and with 4 patients who interrupted VNS due to behavioural problems
[98]. A recent report on the efficacy of VNS in 5 children with mitochondrial
electron transport chain deficiencies described no significant seizure reduc-
tion in any of the children [99]. Also a study in patients with previous resective
epilepsy surgery showed a limited seizure suppressing effect of VNS [100]
although another report described improved seizure control in this specific
patient group [101]. A study of Sirven *et al.* included 45 patients who were
50 years of age and older. 31/45 patients had a follow-up of 1 year, with a
reported responder rate of 68%, good tolerance and improvement of quality of
life scores [102].

Safety, side effects and tolerability

Safety concerns with regard to VNS treatment can be approached from different angles. As the device needs to be implanted, a surgical intervention is required. The effects of delivering current to nervous tissue need to be considered as this might provoke changes in innervated organs and result into acute or chronic side effects. Patients with refractory epilepsy are often young people. The potential teratogenic effects of this new treatment have to be examined. The implanted device and wires have to be examined for MRI compatibility.

Perioperative side effects

The classical surgical technique has been described in detail by several authors [103–105]. Surgical techniques using a single cervical incision and sub-pectoral placement have also been described resulting in favourable cosmetic outcome in adults and children without prolonging the duration of the procedure [68, 106, 107]. Cosmetic side effects have also been improved since the production of the smaller Model 101 and will be greatly improved once the Model 103 Generator Demipulse and Model 104 Generator Demipulse Duo become widely available. Dimensions of the different VNS Therapy™ are shown in Fig. 2. In the initial description of the implantation technique, Reid recommends general anaesthesia until the surgeon is comfortable with the approach [103]. The procedure should be carried out by a neurosurgeon familiar with the surgical approach for carotid endarterectomy because of the location of the vagus nerve in the neck in the carotid sheath between the carotid artery and the internal jugular vein. Surgical complications and difficulties are rare. Fluid accumulation at the generator site with or without associated infection occurs in 1–2% of patients and may respond to aspiration and antibiotics. Incisional infections are unusual and usually respond to oral antibiotic therapy and occur in 3–6% of the patients [6]. Rarely the generator or the electrodes have to be

Model 100	Model 101	Model 102/102R	Model 103/104
Thickness: 0.52″ (13.2 mm)	0.41″ (10.3 mm)	0.27″ (6.9 mm)	0.27″ (6.9 mm)
31 cc	26 cc	14/16 cc	8/10 cc

Fig. 2. Evolution in VNS Therapy pulse generators

removed. Some centers use prophylactic antibiotic treatment. This was done in the EO3 study and no infections were reported. In the EO5 study, infection led to device removal in 3/198 patients.

Patel *et al.* reviewed 11 cases of vagal nerve stimulator pocket infections in children. In all patients device removal was required to cure the infection [108]. Lower facial weakness is a side effect that was reported in 2 patients from EO3 and 2 from EO5 [56, 57]. It was attributed to high surgical incisions that are made to connect the electrode to the vagus nerve. With improvement of surgical techniques this side effect has not been reported since. Unilateral vocal cord paralysis occurred after approximately 1% of the implants in the controlled studies with full recovery after a few weeks in most cases. This may be due to intraoperative manipulation of the vagus nerve and subsequent damage to the vagal nerve vascularization [109]. One patient intended to enter the EO1 study, experienced a partial vocal cord paralysis due to nerve oedema [110]. This was considered a surgical complication as sutures, meant to aid at manipulating the helical electrodes, had been tied around the vagus nerve. Upon revision, the nerve was noted to have an oedematous aspect. Return to normal function occurred after removal. Left vocal cord paralysis occurred in 1 patient in the EO3 study and resolved when a malfunctioning device was removed. In two patients this complication was reported in the EO5 study. One recent study systematically evaluated vocal fold mobility in subjects before and after implantation. Thirteen patients underwent pre-implantation laryngeal electromyography and videolaryngoscopy. Two weeks after implantation and three months after implantation and activation of the device all subjects were revaluated. Perioperative vocal fold paresis occurred in approximately 50% of subjects [110].

Ramping up and long-term stimulation

For therapeutic purposes, VNS aims at stimulating vagal afferents. There are wide spread connections from the vagus nerve to the central nervous system. Through these connections efficacious stimulation parameters may also induce other central nervous system side effects. Moreover, selectively stimulating afferents is difficult and approximately 20% of the fibers in the cervical part of the vagus nerve are efferent fibers. These fibers innervate thoracoabdominal organs, which explains the potential serious side effects when these fibers are stimulated [111]. Certain side effects related to undesired stimulation of nerve fibers might be immediately perceptible by the patient. The main efferent innervation of the vagus nerve serves to monitor and modulate visceral activity. These autonomic processes are usually not perceived by the patient. There may also be side effects specifically related to chronic stimulation that will cause symptoms and become clinically apparent only after long-term treatment. The most prominent and consistent sensation in patients when the vagus nerve is stimulated for the first time, even at low output current levels, is a tingling

sensation in the throat and hoarseness of the voice. The tingling sensation may be due to secondary stimulation of the superior laryngeal nerve that branches off from the vagus nerve superior to the location of the implanted electrode but travels along the vagus nerve in the carotid sheath [112]. The superior laryngeal nerve carries sensory fibers to the laryngeal mucosa. Stimulation of the recurrent laryngeal nerve that branches off distally from the location of the electrode and carries motor ($A\alpha$) fibers to the laryngeal muscles causes the stimulation-related hoarseness [113, 114]. Fiberoptic laryngoscopy and video stroboscopic examination have shown left vocal cord adduction (tetanic contraction) during stimulation at 30 Hz or higher [114–118]. These stimulation related side effects are dose dependent which means that higher amplitudes, higher frequencies and wider pulse widths are associated with more intense sensations and voice changes [55]. With regard to side effects related to stimulation of vagal efferents, effect on heart rate and gastrointestinal digestion are of major concern. Stimulation of the efferent fibers may induce bradycardia and hypersecretion of gastric acid. The stimulation electrode is always implanted on the left vagus nerve, which is believed to contain fewer sinoatrial fibers than the right. It has been suggested that the electrode is implanted below the superior cardiac branch of the vagus nerve. In primates, including man, however, the most cranial efferents arise from the recurrent laryngeal branch of the vagus, which is distal to the electrode site and should consequently be activated by stimuli above their treshold [113, 119]. In the initial pilot trials and controlled randomised trials extensive internal investigations were performed, including continued monitoring in the long-term extension phases. With regard to potential central nervous system side effects related to stimulation of vagal afferents and their connections in the brainstem and cerebral hemispheres, some studies were performed to evaluate changes in EEG, sleep stages, balance and cognition. In most studies systematic AED plasma monitoring was performed. In the EO1 and EO2 studies there were no effects on heart rate after 3 months of stimulation as measured by electrocardiography (ECG) and Holter monitoring and no effects on gastric acid output as measured by fasting acid output during 1 h. There were no changes in the physical examinations, specifically systolic and diastolic blood pressure and body weight. There was no effect on AED serum levels [55]. EEG during sleep, anaesthesia and wakefulness was not affected [120]. Side effects reported by the patients in the EO1 and EO2 study were almost always related to the stimulation on-time and consisted of hoarseness and tingling sensation, left anterior neck muscle movement, hiccup, cough, shortness of breath during exercise [55]. Some of these side effects such as muscle movement may be due to collateral spread of current stimulating nervous structures in the vicinity of the vagus nerve [121]. Such events are often triggered by a certain posture e.g. head turning to the left or left lateral decubitus and may be relieved by changing position. In the EO3

study stimulation-related hoarseness was present in 1/3 of the patients, coughing and throat pain also gained statistical significance [111]. Hoarseness was significantly more present in the HIGH stimulation group. No cardiac or gastrointestinal side effects were present. Twenty-four-hour Holter monitoring in 28 patients (11 from the HIGH stimulation group, 17 from the LOW stimulation group) showed no VNS-related abnormalities [56]. One patient with mild hypercholesterolemia had a nonfatal myocardial infarction following 8 weeks of VNS. The relationship between this event and VNS is uncertain. In 14 patients, gastric acid output was measured showing a non-significantly increased basal gastric acid output during VNS that had no clinical correlate. There were no reports of gastric ulcers and no significant changes in pulse, respiration, blood pressure, temperature or weight [111]. Pulmonary function testing in a subgroup of 15 patients showed no influence of VNS on the forced expiratory volume after 3 and 9 months of stimulation [122]. In one patient with obstructive lung disease airflow obstruction occurred after increasing the stimulation parameters. Obstructive lung disease was considered a relative contraindication for VNS. Also patients with pre-existing obstructive sleep apnoea are at risk for increase of nightly apnoeas [123]. Reduction of stimulation frequency may prevent exacerbation of the condition. In the EO3 study, mean AED plasma concentrations during VNS were similar on monthly visits. In the EO5 study, a similar side effect profile was found [57]. One patient in the HIGH stimulation group had a compromised postictal respiration pattern, which led to device deactivation. In the extension phase, the device was restarted without problems. No other pulmonary function problems, as assessed by pulmonary function tests, were observed. Ninety-nine percent of patients completed the EO5 study indicating high tolerability for the treatment [57]. A notable increase of the perceived well-being during VNS treatment was found using a Global rating scale for quality of life scored by the patient, the investigator and a companion. In the patient series of 118 patients, 4 patients requested the stimulator to be turned off due to lack of efficacy. In none of the patients the device had to be turned off due to stimulation-related side effects. In the long-term extension trials, the most frequent side effects were hoarseness in 19% of patients and coughing in 5% of patients at 2 years follow-up; shortness of breath in 3% of patients at 3 years [60]. There was a clear trend towards diminishing side effects over the 3-year stimulation period. Ninety-eight percent of the symptoms were rated mild or moderate by the patients and the investigators [124]. Side effects can usually be resolved by decreasing stimulation parameters. Central nervous system side effects typically seen with AEDs were not reported. After 3 years of treatment, 72% of the patients were still on the treatment [60]. The most frequent reason for discontinuation was lack of efficacy. Holter monitoring in a sample of patients of the EO4 study showed no clinically symptomatic changes. Pulmonary function testing was performed

in 124 patients with no change between baseline and long-term treatment [59]. Initial studies on small patient groups treated for 6 months with VNS showed no negative effect on cognitive motor performance and balance [125–127]. These findings were confirmed in larger patient groups with a follow-up of 2 years [128, 129]. Hoppe *et al.* showed no changes in extensive neuropsychological testing in 36 patients treated for 6 months with VNS [130]. In patients treated for 3 months with VNS who underwent polysomnography and multiple sleep latency testing there was no change in sleep architecture and a marked decrease in daytime sleepiness was noticed [131]. After that, several studies investigated the effect of VNS on sleep and respiration and found no major respiratory changes [114], hypocapnia [59, 132], apneas [124, 133–136], a decrease in SaO_2 [137] and modification of the sleep structure [138]. A survey of 20 patients who responded to a questionnaire specifically addressing the issue of voice change showed that 95% of the patients experience some kind of voice change but that 100% would have a stimulator reimplanted knowing the vocal side effects they have [114]. Three studies investigated whether the effect on the vocal cord and laryngeal muscles influenced swallowing in the sense that orally ingested material could enter the subepiglottal larynx [71, 139, 140]. This could lead to aspiration and pneumonia. Using therapeutic VNS parameters there were no clinically significant swallowing problems. However, patients with severe mental and motor impairment, pre-existing dysphagia and benzodiazepine treatment might be at risk for swallowing problems during VNS on-time [71]. VNS can be interrupted during meals using the magnet feature although this was experienced as impractical by the parents of two patients on a long-term basis. One study investigated the effects of chronic VNS on visceral vagal function and found no significant adverse effect on gastrointestinal vagal function [141]. Despite the fact that the initial studies showed no clinical effect on heart rate, occurrence of bradycardia and ventricular asystole during intra-operative testing of the device (stimulation parameters: 1 mA, 20 Hz, 500 μs, ~17 s) have been reported in a few patients. None of the reported patients had a history of cardiac dysfunction, nor did they show abnormal cardiac testing after surgery. Tatum *et al.* reported on 4 patients who experienced ventricular asystole intraoperatively during device testing [142]. In 3 patients, the implantation procedure was aborted. In one patient a rechallenge of stimulation with incremental increases from 0.25 to 1 mA did not reveal a reappearance of bradycardia. Implantation was completed and no further cardiac events were noticed after start of VNS. Asconape *et al.* reported on a single patient who developed asystole during intra-operative device testing. After removal of the device, the patient recovered completely [121]. Ali *et al.* described 3 similar cases. Cardiac rhythm strips were available and showed a regular 'p'-wave (atrial rhythm) with no ventricular activity indicating a complete AV nodal block. In two of these patients the device was subsequently

removed. In one patient the device was left in place without experiencing any other adverse events after start of VNS [143]. Andriola *et al.* reported on 3 patients who experienced an aystole during intraoperative lead testing and who were subsequently chronically stimulated [144]. Ardesch *et al.* reported on 3 patients with intraoperative bradycardia and subsequent uneventfull stimulation [145]. Possible hypotheses with regard to the underlying cause are inadvertent placement of the electrode on one of the cervical branches of the vagus nerve or indirect stimulation of these branches, reversal of the polarities of the electrodes which would lead to primary stimulation of efferents in stead of afferents, indirect stimulation of cardiac branches, activation of afferent pathways affecting higher autonomic systems or of the parasympathetic pathway with an exaggerated effect on the atrioventricular node, technical malfunctioning of the device or idiosyncratic reactions. The contributing role of specific AEDs should be further investigated. Suggested steps to be taken in the operating room in case of bradycardia or asystole during generator and lead impedance testing have been formulated by Asconape *et al.* [121]. Adverse cardiac complications at start or during ramping-up of the stimulation intensity have not been observed [111]. Very recently, one case report described a late onset bradyarrhythmia after 2 years of vagus nerve stimulation [146].

Annegers *et al.* have reported on 25 deaths in 1819 patients treated with VNS. SUDEP rates were 4.1 in the VNS group versus 4.5 per 1000 for patients with refractory epilepsy. Within the VNS treated patients, SUDEP rates dropped from 5.5 per 1000 for the first 2 years of treatment to 1.7 per 1000 for the subsequent years suggesting a trend towards lower SUDEP rates in refractory epilepsy patients treated with VNS [147].

Table 3. *Suggested steps in case of intraoperative bradycardia and/or asystole [124]*

1. Verfiy that electrodes are placed on the vagus nerve
2. Locate the cervical branches to assure that electrodes are placed distally to their origin
3. Verify device polarity
4. Check that the leads are well seated into position and securely locked into the generator with the setscrews
5. Check for saline or blood pool around the lead's stimulation coils
6. Repeat stimulation at lower settings eg. 0.25 mA, 20 Hz, 250 μs, 14 s
7. Use recorded ECG strip
8. Proceed gradually to step up stimulation according to tolerance
9. Consider using silastic dam to insulate against collateral stimulation of cardiac brances
10. Defer starting prolonged VNS for two weeks after implantation to minimize collateral current spread

Miscellaneous side effects

In the literature there are several case reports on isolated adverse events [148–156]. A summary of these events is given in Table 4.

Psychiatric side effects have been reported by Blumer *et al.* who found an exacerbation of preexisting dysphoric disorders in patients with a >75% reduction in seizure frequency after treatment with VNS [157]. This 'forced normalization' appeared to occur more often when compared with AED treatment and can be successfully treated with antidepressant medication. It might also be related to the VNS-induced increase of alertness that is often reported and is unrelated to changes in seizure frequency. In patients with pre-existing psychiatric disorders decreased sedation and increased alertness may manifest itself as psychosis with hallucinations. Also De Herdt *et al.* reported on 4 cases of psychosis after VNS treatment [158]. In contrast to an increase in psychiatric disturbances, Koutroumanidis suspected a potential antipsychotic effect in patients with postictal psychosis. These symptoms disappeared in two patients who were treated with VNS following unsuccessful epilepsy surgery [100]. There are clear indications that VNS can interfere with psychiatric symptoms and that specific VNS-induced 'positive' side effects exist.

MRI/3 Tesla MRI

Most patients with refractory epilepsy who are treated with VNS have previously undergone MRI during the presurgical evaluation. It is not uncommon for such patients to require MRI after VNS implantation to further monitor underlying neurological diseases e.g. in case of unexplained increase in seizure frequency, follow-up of intracranial lesions and also for MRI indications as in the general population. Based on laboratory testing using a phantom to simulate a human body, the VNS Therapy™ system device is labelled MRI compatible when used with a send and receive head coil [159]. In addition to the safety issues, there was no significant image distortion [160]. A retrospective analysis of 27 MRI scans performed in 25 patients at 12 different centers was performed in order to confirm the findings from the experimental set-up in a clinical series. All patients were scanned on a 1.5 Tesla machine. On one occasion a body coil was used. Three scans were performed with the stimulator in the on-mode. One patient reported a mild voice change for several minutes; one child reported chest pain and claustrophobia. Twenty-three patients reported no discomfort around the lead or the generator. It was concluded that MRI is safe as long as guidelines stated in the Physician's manual of the implanted device are followed. In these guidelines it is suggested to program the pulse generator output current to 0 mA. On one occasion this has led to the occurrence of a generalized status epilepticus in a patient who was well controlled with an output current of 2 mA. The authors of the report recom-

Table 4. *Miscellaneous side-effects*

Author	Side effect	Patients	Time of occurrence	Stimulation parameters	MOA
Kim et al. [148]	Horner syndrome	6 year-old	postoperative surgical continuous	unavailable	transient dysfunction of the oculosympathic fibers within the carotid sheath
Iriarte et al. [156]	episodic torticollis tonic contraction left SCM	20 year-old man	during stimulation on-time	30 Hz, 500 μs, 1 min on, 5 min off, 2 mA	electrical activation of motor fibers of SCM or of N. XI by proximity or antidromal through ramus internus or anatomic variant connecting N. X–XI
Sanossian and Haut [149]	chronic diarrhea	35-year old man	one week after VNS initiation	0.25–0.75 mA, 30 Hz, 500 μs, 30 s on, 5 min off	idiosyncratic reaction in patient with pre-existing hemorrhoids or variability in number of vagal lefferents
Leijten and van Rijen [150]	dyspnoe and cabdominal discomfort in supine position with head turned to the left	42-year old man	several months after VNS initiation, during stimulation on-time in specific head position	2–2.25 mA, 30 Hz, 500 μs, 30 s on, 5 min off	leakage current coactivated the phrenic nerve that is approximated to the vagus nerve when head is turned to the left
Koutroumanidis et al. [151]	aggravation of epilepsy and appearance of a new seizure type	20-year old woman	4 months after VNS initiation, 2 days after output current increase	2.5 mA, 30 Hz, 500 μs, 30 s on, 5 min off	breakdown of inhibitory mechanisms in specific functional and structural neuronal networks, facilitating discharge propagation

(*continued*)

Table 4 (continued)

Author	Side effect	Patients	Time of occurrence	Stimulation parameters	MOA
Gatzonis et al. [152]	pyschosis, schyophrenia-like syndrome	35-year old man	3 months after VNS initiation, at time seizure control was reached	1.5 mA, 30 Hz, 500 μs, 30 s on, 5 min off	forced normalization
Kalkanis et al. [153]	self-inflicted delayed-onset vocal cord paralysis	20-year old woman with MR	15 days after surgery = VNS initiation	1 mA, 30 Hz, 500 μs, 30 s on, 5 min off	self-infliced injury to the vagus nerve from external manipulation of the device = 'Twiddler's syndrome' developmental disability: risk factor
		25-year old man with MR	6 days after surgery = VNS initiation	1 mA, 30 Hz, 500 μs, 30 s on, 5 min off	
Rauchenzauner et al. [154]	NT-proBNP levels increased during VNS and seizures	4-year old boy	One year after VNS implantation	2,5 mA, 30 Hz, 250 μs, 30 s on, 5 min off	Unspecific activation of the neuro-cardio-endocrine system
Guilfoyle et al. [155]	adjustment of a Strata valve shunt by magnet and subsequent underdrainage of CSF	14-year old girl	After 6 months of VNS	unavailable	Susceptibility of strata valves to strong magnetic fields

MOA Mechanism of action, *opthalm* ophtalmological *SCM* sternocleidomastoid, *N XI* 11th cranial nerve = acessory nerve, *N. X* 10th cranial nerve = vagus nerve, *SE* side effect, *RX* radiography, *CPS* complex partial seizure, *CSWSS* continuous spike waves during slow sleep, *MR* mental retardation.

mend that intravenous access should be obtained and a benzodiazepine should be either available or pre-administered in patients with a well defined response who are undergoing elective MRI and in whom the generator is acutely programmed to 0 mA. Functional MRI (fMRI) is a recently developed technique that allows non-invasive evaluation of cerebral functions such as finger movements and language [161]. It has been widely used for research but is currently increasingly applied to evaluate functional tissue in the neighbourhood of lesions before resective surgery and also for assessing language dominance in the presurgical evaluation of epilepsy patients [5, 162]. When fMRI in patients with VNS is used for research purposes to evaluate VNS-induced changes in cerebral blood flow, scanning should be performed in the on-mode. To prevent the device to be turned off during scanning, an adjustment in the surgical positioning of the device is necessary. The device should be positioned so that the electrode pins that are plugged into the generator are parallel instead of perpendicular to the long axis of the body [163]. There have been several studies in patients treated with VNS for epilepsy as well as for depression showing that fMRI is safe and feasible [164–167]. These studies were performed to elucidate the mechanism of action of VNS and will be discussed later in this study. The use of body coils may be indicated in patients requiring spinal MRI. When removal of electrodes is indicated e.g. due to insufficient efficacy, complete removal is recommended over cutting the distal edges and leaving the electrode in place [168]. Full removal of the electrodes allows potential future MRI with body coils. Heating of the electrodes is related to the lead length. If full removal of the electrodes is difficult the leads should be cut to less than 10 cm. In several of our patients uneventful MRI was performed according to the prescribed precautions. In one patient with frequent simple partial seizures successful and uneventful fMRI was performed with the stimulator in the off-mode.

Teratogenic effects of VNS

Teratogenic effects in the sense of deleterious effects on the development of an embryo or foetus seem unlikely due to an implanted device. One study investigated teratogenicy of VNS in rabbits [169]. There were no effect of VNS on any reproductive parameter including mating behaviour, number of matings required, viable and dead foetuses, litter size, individual kit weights and organ weights. Histological assessment did not reveal any changes or abnormalities in selected tissues including neural tissues. Pregnancy is a particular situation especially in women with epilepsy and even more so when the epilepsy is refractory. Women with refractory epilepsy are often treated with several antiepileptic treatments of which VNS may be one. There are no known AEDs/VNS interactions outside pregnancy so VNS-induced changes in AED blood levels with loss of seizure control seem unlikely. In 1998 Ben-Menachem

reports on 8 pregnancies in patients treated with VNS after retrospective analysis of ± 1000 patients [170]. All patients were taking concomitant AEDs. Five pregnancies went full term resulting in unremarkable and healthy deliveries including one set of twins. Two elective abortions due to unplanned pregnancy and abnormal in utero foetal development respectively were performed. The abnormal development was attributed to AEDs. One patient reported spontaneous abortion although the actual pregnancy was never confirmed. It appears that VNS does not inhibit conception.

Discussion

Despite the fact that VNS is accepted in epilepsy centers worldwide as a valuable and reliable therapeutic option for patients who are unsuitable candidates for resective surgery, some specific issues remain to counteract its full therapeutic potential. From a clinical point of view, prospective randomized trials investigating long-term efficacy in comparison to other therapeutic options for patients with refractory epilepsy are still lacking. An ongoing multi-center randomized trial called PulSE is currently recruiting patients worldwide and may shed light on the exact position of VNS. Moreover in this trial, the so called 'positive side effects' of VNS are being investigated in a standardized way which may provide us with more objective data with regards to the effect of VNS on mood and quality of life. On the basis of currently available data the responder rate in patients treated with VNS is not substantially higher compared to recently marketed anti-epileptic drugs. Efforts to decrease the number of non-responders may increasingly justify implantation with a device. To increase efficacy, research towards the elucidation of the mechanism of action is crucial. In this way rational stimulation paradigms may be investigated. With a rapidly evolving biomedical world, various neurostimulation modalities will be applied in patients with refractory epilepsy. Future studies will have to show the precise position of VNS in comparison to treatment such as deep brain stimulation and transcranial magnetic stimulation.

Both from the clinical experience with VNS for epilepsy and other pathological conditions and from the research on the mechanism of action, interesting new ideas have arisen to increase clinical efficacy to explore the MOA and to identify different indications for VNS. Further elucidation of the mechanism of action of VNS may help to improve clinical efficacy. Animal research should be directed towards the identification of a useful model to evaluate the seizure suppressing effects of VNS. The initial experiments investigating VNS in the pentylenetetrazol and MES model prove difficult to be reproduced even in hands of experienced researchers. In Ghent University Hospital, VNS has shown efficacy in the motor cortex stimulation model. The seizure threshold in this animal model significantly increases following one hour of VNS. This

model can now be further applied to investigate the efficacy of different stim-
ulation parameters. Apart from the acute seizure suppressing effects of VNS,
the more chronic and estimated neuromodulatory effects should be further
investigated in the laboratory. Investigating VNS in a chronic setting requires
efforts to investigate animals in chronic conditions with specifically designed
electrodes that allow long-term treatment. At Ghent University Hospital a
chronic video-EEG monitoring unit with customised miniature vagus nerve
electrodes has been designed for this purpose. Chronic epilepsy models that
may be used are the genetic absence epilepsy model (GAERS). Despite the
fact that absence seizures are generally benign and easily controlled with anti-
epileptic drugs, investigation of efficacy of VNS in the GAERS model may
contribute to the identification of specific brain structures that are implicated
in the MOA of VNS. Preliminary studies using the kindling model have been
published. Ongoing work at Ghent University Hospital, is investigating the
long-term effects of VNS in the rapid kindling model. The ultimate goal may
be to investigate the efficacy of VNS in spontaneous seizures as observed in
status epilepticus model or the kainate model. Hints towards involvement of
specific neurotransmitters in VNS have been found. Further investigation of
this topic may be performed using microdialysis techniques in different ani-
mal models.

   With regards to research in humans, prospective studies such as the PulSe
study may further elucidate the outcome of VNS as it is being used in a day
to day clinical practice at the moment. Within the currently used VNS param-
eters many combinations are possible and the efficacy of different par-
adigms should be investigated in a prospective way to evaluate potential
superiority of certain paradigms with regards to efficacy as well as battery
life. A multicenter study between Ghent University Hospital, Dartmouth
Hitchcock Medical center and Montevideo Neurological Hospital is currently
investigating these issues. Because of the variability of different phenotypes of
epilepsy, it seems simplistic to assume that there are specific combinations of
stimulation parameters that will optimally benefit all different types of epilep-
sy and all refractory individuals. Individually guided stimulation parameter
titration may be a more successful avenue. Research should therefore be
directed towards finding non-invasive measures that can guide individual
titration. Neurophysiological investigation such as evoked potentials and
EEG recording especially would be very tempting tools. Interesting research
lines include the investigation of VNS efficacy in specific epilepsy conditions
and in other neurological conditions. Case reports on the efficacy of VNS in
status epilepticus are encouraging and require further prospective studies in
larger patients groups. From a more experimental view, VNS may be consid-
ered as part of a closed-loop system where triggered VNS is performed on a
more indivualized basis. Research towards the development of transcutane-

ous systems may allow identifying predictive factors for response before chronic implantation is performed.

Conclusion

Patients with refractory epilepsy present a particular challenge to new therapies. VNS has demonstrated to be an efficacious and safe treatment. 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. VNS seems equally efficient for children. The degree of improvement in seizure control from VNS remains comparable to new antiepileptic drugs. Contrary to treatment with AEDs, efficacy has a tendency to improve with longer duration of treatment up to 18 months postoperatively. 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 may result from this.

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