

## Neurostimulation as a Treatment Option for Epilepsy

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### Abstract

Although neurostimulation is not a new treatment modality, it is an emerging treatment for various neurological diseases. Currently available pharmacological and surgical treatments leave about 30% of patients not seizure-free. Electrical stimulation of the 10th cranial nerve or vagus nerve stimulation (VNS) is an extracranial type of stimulation that is currently routinely available. Through an implanted device and electrode, electrical pulses are administered to the afferent fibres of the left vagus nerve in the neck. VNS is indicated in patients with refractory epilepsy who are unsuitable candidates for epilepsy surgery or who have had insufficient benefit from such a treatment. Intracerebral neurostimulation requires accessing the intracranial nervous system as stimulation electrodes are inserted into intracerebral targets for deep brain stimulation (DBS) or placed over the cortical convexity for cortical stimulation (CS). Recently, trials with DBS in different intracerebral structures such as the thalamus, the subthalamic nucleus and medial temporal lobe structures have been performed. CS ± DBS in a closed-loop system (responsive neurostimulator system [RNS]) is currently being investigated in a multicentre trial. It is likely that neurostimulation for epilepsy will become a more practical and more widely used treatment modality for patients with refractory epilepsy.

### Keywords

Neurostimulation, seizures, refractory epilepsy, therapeutic stimulation

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### Vagus Nerve Stimulation

Electrical stimulation of the 10th cranial nerve or vagus nerve stimulation (VNS) has become a valuable option in the therapeutic armamentarium of adults and children with refractory epilepsy. Since its introduction in 1989 over 50,000 patients have been treated with VNS worldwide. Efficacy, side effects and tolerability have been extensively studied. The precise mechanism of action remains to be elucidated, but some essential intracerebral pathways have been identified.<sup>1</sup>

### Clinical Efficacy

In the early 1990s, initial results from two single-blinded pilot clinical trials (phase I trials EO1 and EO2) in a small group of patients with refractory complex partial seizures from three epilepsy centres in the US were reported.<sup>2–5</sup> In nine out of 14 patients treated for three to 22 months, a reduction in seizure frequency of at least 50% was observed.<sup>6</sup> Complex partial seizures, simple partial seizures and secondary generalised seizures were affected. It was noticed that reduction in the frequency, duration and intensity of seizures lagged four to eight weeks after the initiation of treatment.<sup>2</sup> In the meantime, two prospective multicentre (n=17) double-blind randomised studies (EO3 and EO5) were started including patients from centres in the US (n=12), Canada (n=1) and Europe (n=4).<sup>7–11</sup> The results of EO3 in 113 patients showed a 24% decrease in seizures in the treatment group versus 6% in the control group after three months of treatment. The number of patients was insufficient to achieve US Food and Drug Administration (FDA) approval,

leading to the EO5 study of 198 patients in the US. Ninety-four patients in the treatment group had a 28% decrease in seizure frequency versus 15% of patients in the control group.<sup>11</sup>

The controlled EO3 and EO5 studies had their primary efficacy end-point after 12 weeks of VNS. Increased efficacy with longer treatment was found in all published reports on long-term results.<sup>12–16</sup> The mean reduction in seizure frequency increased up to 35% at one year and up to 44% at two years of follow-up. After that, improved seizure control reached a plateau.

In the following years, other large prospective clinical trials were conducted in different epilepsy centres worldwide. In Sweden, long-term follow-up in the largest patient series (n=67) in one centre 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 five years.<sup>17</sup> A joint study of two epilepsy centres in Belgium and the US included 118 patients with a minimum follow-up duration of six months. They found a mean reduction in monthly seizure frequency of 55%.<sup>18</sup> Long-term seizure freedom was achieved in only a small minority of patients (7%). In China, a mean seizure reduction of 40% was found in 13 patients after 18 months of VNS.<sup>19</sup> From a clinical point of view, prospective randomised trials investigating long-term efficacy in comparison with other therapeutic options for patients with refractory epilepsy are still lacking.

## Children

There are no controlled studies of VNS in children, but many epilepsy centres 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.<sup>20-25</sup> Rare adverse events unique to this age group included drooling and increased hyperactivity.<sup>24</sup> In children with epileptic encephalopathies, efficacy may become evident after only >12 months of treatment.<sup>25</sup> More recent reports show slightly better seizure control with VNS in children compared with adults. Fifty-four per cent of children in a series of 26 from Australia responded to VNS with ≥50% seizure frequency reduction. Status epilepticus episodes were reduced or ceased in four patients with recurrent status epilepticus.<sup>26</sup>

## Seizure Types and Syndromes

The open-label longitudinal multicentre EO4 study also included patients with generalised epilepsy (n=24).<sup>27,28</sup> In these patients overall seizure frequency reduction was 46%. Quintana et al.,<sup>29</sup> Michael et al.<sup>30</sup> and Kostov et al.<sup>31</sup> described in a retrospective manner that primary generalised seizures and generalised epilepsy syndromes responded equally well to VNS compared with partial epilepsy syndromes. A prospective study by Holmes et al. in 16 patients with generalised epilepsy syndromes and stable antiepileptic drug (AED) regimens showed an overall mean seizure frequency reduction of 43% after a follow-up of at least 12 months.<sup>32</sup> Ben-Menachem et al. included nine patients with generalised seizures in a prospective long-term follow-up study. The patients with absence epilepsy in particular had a significant seizure reduction.<sup>17</sup>

A few studies are available specifically describing the use of VNS in patients diagnosed with Lennox-Gastaut syndrome. One prospective study in 16 patients with Lennox-Gastaut syndrome found that one-quarter of patients had a >50% reduction in seizure frequency after six months of follow-up, comparable to the response rates in the controlled studies, which included a few patients with leaky gut syndrome (LGS).<sup>33</sup> Other prospective studies reported higher responder rates with a >50% seizure frequency reduction in half of the patients (n=13, six-month follow-up),<sup>34</sup> in six out of seven patients (six-month follow-up)<sup>35</sup> and in seven out of nine patients (one- to 35-month follow-up).<sup>36</sup> A retrospective multicentre study in 46 patients with LGS reported responder rates of 43%.<sup>37</sup> Kostov et al. reported on 30 patients with Lennox-Gastaut syndrome. The best effects were observed with atonic seizures (80.8% median reduction), followed closely by tonic seizures (73.3% median reduction). Additional positive effects included milder or shorter ictal or post-ictal phases in 16 patients. Improved alertness was reported in 76.7%.<sup>38</sup>

There have been many reports on various other seizure types and syndromes, such as seizures in patients with hypothalamic hamartomas,<sup>39</sup> tuberous sclerosis,<sup>40,41</sup> progressive myoclonic epilepsy,<sup>42,43</sup> Landau Kleffner syndrome,<sup>44</sup> Asperger's syndrome,<sup>45</sup> epileptic encephalopathies<sup>39</sup> and syndromes with developmental disability and mental retardation<sup>46-49</sup> and infantile spasms.<sup>50</sup> All of the studies reported were limited to reasonable efficacy in terms of controlling seizures and other disease-related symptoms, such as cerebellar dysfunction and behavioural and mood disturbances. A report on the efficacy of VNS in five children with mitochondrial electron transport chain deficiencies described no significant seizure reduction in any of the children.<sup>51</sup> Furthermore, a study in patients with previous resective epilepsy surgery showed a limited seizure-

suppressing effect of VNS,<sup>52</sup> although another report described improved seizure control in this specific patient group.<sup>53</sup>

## Side Effects and Tolerability

Even at current low output levels, the most prominent and consistent sensation in patients when the vagus nerve is stimulated for the first time is a tingling sensation in the throat and hoarseness of the voice due to secondary stimulation of the superior laryngeal nerve.<sup>54-56</sup> In long-term extension trials, the most frequent side effects were hoarseness in 19% of patients and coughing in 5% of patients at two-year follow-up and shortness of breath in 3% of patients at three years.<sup>15</sup> There was a clear trend towards diminishing side effects over the three-year stimulation period. Ninety-eight per cent of the symptoms were rated mild or moderate by the patients and the investigators.<sup>57</sup> Side effects can usually be resolved by decreasing stimulation parameters. Central nervous system side effects seen typically with AEDs were not reported. After three years of treatment, 72% of the patients were still on the treatment.<sup>15</sup> The most frequent reason for discontinuation was lack of efficacy. Initial studies on small patient groups treated for six months with VNS showed no negative effect on cognitive motor performance and balance.<sup>58-60</sup> These findings were confirmed in larger patient groups with a follow-up of two years.<sup>61,62</sup> Hoppe et al. showed no changes in extensive neuropsychological testing in 36 patients treated for six months with VNS.<sup>63</sup>

## Cardiac Side Effects

Despite the fact that the initial studies showed no clinical effect on heart rate, occurrence of bradycardia and ventricular asystole during intraoperative testing of the device (stimulation parameters: 1mA, 20Hz, 500µs, ~17 seconds) has been reported in a small number of patients. None of the reported patients had a history of cardiac dysfunction or abnormal cardiac testing after surgery. Tatum et al. reported on four patients who intraoperatively experienced ventricular asystole during device testing.<sup>64</sup> In three patients, the implantation procedure was aborted. Asconape et al. reported on a single patient who developed asystole during intraoperative device testing. After removal of the device, the patient recovered completely.<sup>65</sup> Ali et al. described three similar cases.<sup>66</sup> Andriola et al. reported on three patients who experienced an aystole during intraoperative lead testing and who were subsequently chronically stimulated.<sup>67</sup> Ardesch et al. reported on three patients with intraoperative bradycardia and subsequent uneventful stimulation.<sup>68</sup> Possible hypotheses in terms of 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 instead of afferents, indirect stimulation of cardiac branches, activation of afferent pathways affecting the 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 investigated further. One case report described late-onset bradyarrhythmia after two years of VNS.<sup>69</sup>

## Mechanism of Action

Following a limited number of animal experiments in dogs and monkeys investigating safety and efficacy, the first human trial was performed.<sup>2</sup> To date, the precise mechanism of action (MOA) of VNS and how it suppresses seizures remains to be elucidated. Research directed towards the identification of involved fibres, intracranial structures and neurotransmitter systems has been performed.

Animal experiments and research in humans treated with VNS have collated electrophysiological studies (electromyography [EMG], evoked potential [EP], electroencephalography [EEG]) functional anatomical brain-imaging studies (positron-emission tomography [PET], single-photon-emission computed tomography [SPECT], functional magnetic resonance imaging [fMRI], c-fos, densitometry), and neuropsychological and behavioural studies. Furthermore, from the extensive clinical experience with VNS, interesting clues have arisen concerning the MOA of VNS. 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-fibres.<sup>70,71</sup> Unilateral stimulation influences both cerebral hemispheres, as shown in several functional imaging studies.<sup>72,73</sup> Crucial brainstem and intracranial structures have been identified and include the locus coeruleus, the nucleus of the solitary tract and the thalamus and limbic structures.<sup>74-76</sup> Neurotransmitters playing a role may involve not only the major inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (GABA) but also the serotonergic and adrenergic systems.<sup>77,78</sup> An extensive overview of the MOA of VNS can be found in Vonck et al.<sup>79</sup>

## Deep Brain Stimulation

Deep brain stimulation (DBS) is a more recently explored treatment modality in epilepsy. Compared with VNS it is a more invasive option. Parallel to VNS, the precise MOA and the ideal candidates for this treatment option are currently unidentified. Moreover, it is unknown which intracerebral structures should be targeted to achieve optimal clinical efficacy. Two major strategies for targeting have been followed. One approach is to target crucial central nervous system structures that are considered to have a 'pacemaker', 'triggering' or 'gating' role in the epileptogenic networks that have been identified such as the thalamus or the subthalamic nucleus. Another approach is to interfere with the ictal onset zone itself. This implies the identification of the ictal onset zone, a process that sometimes requires implantation with intracranial electrodes.

## Targets

The selection of targets for DBS in humans partially resulted from progress in the identification of epileptogenic networks.<sup>80</sup> Although the cortex plays an essential role in seizure origin, increasing evidence shows that subcortical structures may be involved in the clinical expression, propagation, control and sometimes initiation of seizures. Consequently, several subcortical nuclei have been targeted in pilot trials for different types of epilepsy. The suppressive effects of pharmacological or electrical inhibition of the subthalamic nucleus (STN) in different animal models for epilepsy and the extensive experience with STN DBS in patients with movement disorders led to a pilot trial of high-frequency (130Hz) continuous STN DBS in five patients by a group from Grenoble.<sup>81,82</sup> Three patients with symptomatic partial seizures had a >60% reduction in seizure frequency. Four other centres have reported STN DBS results. In one patient with Lennox-Gastaut syndrome, generalised seizures were fully suppressed and myoclonic and absence seizures reduced by >75%.<sup>83</sup> Loddenkemper et al. reported seizure frequency reductions of >60% in two out of five patients treated with STN DBS.<sup>84</sup> Handforth et al. reported on one patient with bitemporal seizures in whom half of the seizures were suppressed and in one patient with frontal lobe epilepsy who experienced a one-third reduction of seizures.<sup>85</sup> Vesper et al. described a 50% reduction in myoclonic

seizures in a patient with progressive myoclonic epilepsy in whom generalised seizures had been successfully treated with previous VNS.<sup>86</sup>

Thalamocortical interactions are known to play an important role in several types of seizure. Since 1984, Velasco et al. have investigated a large patient series (n=57) with different seizure types who underwent DBS of the centromedian (CM) nucleus, a structure that can be fairly easily stereotactically targeted due to its relatively large size, its spherical shape and its location on each side of the third ventricle.<sup>87,88</sup> Intermittent (one minute on, four minutes off) high-frequency (60–130Hz) stimulation that alternated between the left and right centromedian (CM) thalamic nucleus was most effective in children (n=5) with *epilepsia partialis continua*, in whom full seizure control was reached between three and four months after stimulation. Secondary generalised seizures in these children were the earliest to respond, after one month of treatment. Atypical absences and generalised seizures (primary or secondary) responded significantly. Three out of 22 patients with Lennox-Gastaut syndrome became seizure-free. Complex partial seizures responded less successfully, although partial improvements were observed after long-term stimulation over one year, and patients tended to be satisfied with the treatment, which significantly decreased or abolished secondary generalised convulsions. In a separate report, Velasco et al. reported on 11 patients with Lennox-Gastaut syndrome, with an overall seizure reduction of 80% and two patients rendered seizure-free.<sup>89</sup>

In a double-blind cross-over protocol performed by Fisher et al., CM thalamic stimulation did not significantly improve generalised seizures in seven patients.<sup>90</sup> An open extension phase of the trial using 24-hour stimulation resulted in a 50% decrease in half of the patients. It has become clear, especially from the experience with VNS but also from other studies, that increased efficacy may be observed after a longer duration of stimulation, possibly on the basis of neuromodulatory changes that take time to develop.<sup>91,92</sup>

There is sufficient evidence to suggest an equally important role of the anterior nucleus (AN) of the thalamus in the pathogenesis of seizure generalisation. Hodaie et al. performed bilateral AN thalamic DBS (one minute on, five minutes off, 100Hz, alternating between right and left AN) in five patients and showed a seizure frequency reduction of between 24 and 89%.<sup>93</sup> Andrade et al. reported on the long-term follow-up of six patients with AN DBS. After seven years of follow-up, five patients showed a more than 50% reduction in seizure frequency.<sup>94</sup> Changes in stimulation parameters over the years did not further improve seizure control. Kerrigan et al. reported that four out of five patients who underwent high-frequency AN DBS showed significant decreases in seizure severity and in the frequency of secondary generalised seizures. Moreover, there was an immediate seizure recurrence when DBS was stopped.<sup>95</sup> These studies all preceded a multicentre double-blind randomised trial of bilateral AN stimulation (Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy [SANTE] trial) in patients with partial-onset seizures with or without secondary generalisation.<sup>96</sup> One hundred and ten patients were enrolled at 17 medical centres in the US. Half received stimulation and half received no stimulation during a three-month blinded phase; all then received unblinded stimulation. In the last month of the blinded phase, the stimulated group had a 29% greater reduction in seizures compared with the control group. Complex, partial and 'most severe' seizures were significantly reduced by stimulation. By two years, there was a median 56% reduction in seizure frequency, 54% of patients had a

seizure reduction of at least 50%, and 14 patients were seizure-free for at least six months. Cognition and mood showed no group differences, but participants in the stimulated group were more likely to report depression or memory problems as adverse events.

The medial temporal lobe region, more specifically the hippocampus, is a rational target for DBS. This region often shows specific initial electroencephalographic epileptiform discharges that can be recorded with invasive EEG electrodes and represent the seizure onset. Temporal lobectomy and, more specifically, selective amygdalohippocampectomy are effective in reducing seizures with a well-defined mesiobasal limbic seizure onset.<sup>97</sup> Basic research involving evoked potential excitability studies in humans and anatomical studies with tracer injections and single-unit recordings with histological studies in animals have also confirmed the involvement of the amygdala and the hippocampus in the epileptogenic network.<sup>98-100</sup> Some studies have applied electrical fields to *in vitro* hippocampal slices with positive effects on epileptic activity.<sup>101</sup> Also, *in vivo* studies in rats have shown that high-frequency stimulation affects seizures in the kindling model.<sup>102</sup> Bragin et al. described repeated stimulation of the hippocampal perforant path in rats showing spontaneous seizures four to eight months after intrahippocampal kainate injection.<sup>103</sup> During perforant path stimulation, spontaneous seizures were significantly reduced. In humans, preliminary short-term stimulation of hippocampal structures showed promising results on interictal epileptiform activity and seizure frequency.<sup>104</sup> Not all patients with temporal lobe epilepsy who underwent resective epilepsy surgery remain seizure-free in the long term. Moreover, temporal lobe resection, especially left-sided, may be associated with memory decline, and temporal lobe resection is contraindicated in patients with bilateral ictal onset. In a pilot trial, 10 patients scheduled for invasive video-EEG monitoring of the medial temporal lobe were offered high-frequency medial temporal lobe DBS following ictal onset localisation.<sup>105</sup> Long-term follow-up in 10 of these patients showed that one out of 10 stimulated patients was seizure-free (>1 year), one out of 10 patients had a >90% reduction in seizure frequency, five out of 10 patients had a seizure frequency reduction of >50%, two out of 10 patients had a seizure frequency reduction of 30–49% and one out of 10 patients was a non-responder. None of the patients reported side effects. In one patient, MRI showed asymptomatic intracranial haemorrhages along the trajectory of the DBS electrodes. None of the patients showed changes in clinical neurological testing.

In four patients with complex partial seizures based on left-sided hippocampal sclerosis, high-frequency stimulation was performed by Tellez-Zenteno et al. in a randomised, double-blind protocol with periods of one month off or on. During the stimulation, on-period seizures decreased by 26% compared with baseline.<sup>106</sup> During the off periods, seizures increased by 49%. Neuropsychological testing revealed no difference between on or off periods, not even in one patient who was stimulated on the left-side following previous right-sided temporal lobectomy. Velasco et al. reported results in 11 patients after 18 months of hippocampal high-frequency stimulation (uni- or bilateral, with or without hippocampal sclerosis on MRI).<sup>107</sup> Patients with normal MRIs showed optimal outcome, with four of them seizure-free after one to two months of stimulation. None of the patients showed neuropsychological decline, with a trend towards improvement.

An implanted responsive neurostimulator system (RNS) is being evaluated for safety and efficacy in a multicentre trial. The device

records cortical EEG signals by means of subdural electrodes and delivers responsive stimulation. Chabolla et al. reported on 18 adults with uni- or bilateral temporal lobe epilepsy who were treated with the RNS and showed a 43 and 53% reduction in seizure frequency, respectively.<sup>108</sup>

## Conclusion

The lack of adequate treatments for all refractory epilepsy patients, the general search for less invasive treatments in medicine and progress in biotechnology have led to an renewed and increasing interest in neurostimulation as a therapeutic option. Apart from the invasive neurostimulation modalities VNS, DBS and cortical stimulation (CS), non-invasive neurostimulation modalities such as transcranial magnetic stimulation, transcutaneous VNS and transcranial direct current stimulation are under investigation. For all types of neurostimulation currently being used and investigated, major problems remain unresolved. The ideal targets and stimulation parameters for a specific type of patient, seizure or epilepsy syndrome are unknown. Long-term side effects need to be investigated further. The elucidation of the MOA of different neurostimulation techniques requires more basic research in order to demonstrate their potential to achieve long-term changes and true neuromodulation.

VNS is a moderately efficacious treatment for patients with refractory epilepsy. It is a broad-spectrum treatment, but identification of specific responders on the basis of type of epilepsy or specific patient characteristics has proved difficult. Large patient groups have been examined, and the identification of predictive factors for response may demand more complex investigations. VNS is a safe treatment and lacks the typical cognitive side effects associated with many other antiepileptic treatments. Moreover, many patients enjoy a positive effect of VNS on mood, alertness and memory. In contrast to many pharmacological compounds, treatment tolerance does not develop in VNS. By contrast, efficacy tends to increase with longer treatment. To increase efficacy, research into the elucidation of the MOA and optimisation of stimulation parameters is crucial.

DBS is evolving from an experimental treatment towards a reasonable treatment option for patients with refractory epilepsy. In addition to several pilot trials in different targets, one randomised controlled trial of DBS in the AN of the thalamus showed that it is a feasible and safe treatment option and that the responder rate is slightly superior to the results of VNS. The precise role of DBS in the treatment of refractory epilepsy remains to be determined. ■



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