The Role of Vagus Nerve Stimulation in the Treatment of Epilepsy

a report by
Alexandra Montavont and Philippe Ryvlin

Department of Functional Neurology and Epileptology, Neurological Hospital, and CTRS-INSERM IDEE (Institute of Child and Adolescent Epilepsies), Hospices Civils de Lyon and Université Claude Bernard Lyon

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Following the first encouraging human trials in 1988, several controlled studies have demonstrated the antiepileptic efficacy of adjunctive vagus nerve stimulation (VNS) in patients suffering from refractory seizures. Accordingly, VNS was approved in Europe in 1994 as an antiepileptic treatment for patients with generalised or focal drug-resistant epilepsy. In 1997, the US Food and Drug Administration (FDA) approved VNS as an adjunctive antiepileptic treatment for patients over 12 years of age suffering from drug-resistant partial epilepsy.

At present, more than 50,000 patients from 24 countries have been treated with VNS, a widely used non-pharmacological treatment for epilepsy. The antiepileptic efficacy of VNS is remarkably consistent among series, with an average decrease in seizure frequency of 40%, a 50% responder rate (i.e. the proportion of patients whose seizure frequency declined by at least 50%) usually ranging between 40 and 50% and a proportion of seizure-free patients below 5%. These figures appear stable over time, with no obvious indication of tolerance, although only a few long-term studies, with a follow-up period of more than three years, have been carried out in adults or in children. One puzzling limitation to the optimal use of VNS is the lack of a factor that reliably predicts its effectiveness.

Whatever the type of epilepsy being considered, VNS is offered only to patients who continue to suffer from refractory seizures despite well-conducted medical treatments. The number of antiepileptic drugs (AEDs) that must be tested before concluding that the epilepsy is drug-resistant remains debatable, but at a minimum of two is required. In practice, the majority of patients treated with VNS have previously received numerous AEDs as both monotherapy and polytherapy. Often, these patients have exhausted all other therapeutic options, including surgery, before VNS is proposed. In terms of the advantages and disadvantages of the various antiepileptic treatments, this strategy is not necessarily the most appropriate.

In this article, we aim to pragmatically address the current indications for VNS against the range of therapeutic, medical and surgical alternatives available for the treatment of refractory epilepsies.

Indications for Vagus Nerve Stimulation in Drug-resistant Partial Epilepsy

Vagus Nerve Stimulation versus Antiepileptic Drugs

No controlled study has directly compared the impact of adjunctive VNS versus AEDs alone in patients with drug-resistant partial epilepsy. Indirect comparison of the 50% responder and seizure-freedom rates observed during placebo-controlled trials suggests that the average efficacy of new-generation AEDs is comparable to that of VNS. However, numerous factors complicate the interpretation of such indirect comparisons, including significant differences in terms of tolerability profile, ease of use, interruption of treatment and delay of efficacy. Globally, VNS offers the advantage of more favourable central nervous system tolerability than AEDs, but at the price of possible aesthetic concerns or intermittent vocal disturbances, with a delay in efficacy that can often be deferred for several months.

It is for this reason that a direct and global comparison of the effects of VNS and AEDs, incorporating quality of life measurements, is needed to assess the respective benefits of these two therapeutic approaches. This is currently being undertaken as part of an international randomised controlled trial, the PuLse study. The rationale for this study rests on the one hand on the observation that, following the failure of three successive AEDs, the addition of a new drug has very little chance of achieving a seizure-free outcome while often being responsible for disturbing side effects, and on the other hand on the notion that VNS might allow a reduction in the number of concomitant AEDs and related side effects. However, recent studies suggest that only a minority of VNS-treated patients experience a significant reduction in their AED load. It is therefore too early to answer the question of whether VNS should be proposed after the failure of only a few AEDs, or instead after all available drugs have been tested.

Vagus Nerve Stimulation versus Resective Surgery

Traditionally, it has been assumed that VNS should be proposed only for those patients who have been rejected for epilepsy surgery. However, this issue may deserve to be challenged and discussed on a case-by-case basis in the two following situations: first, patients who fulfil the criteria of a good surgical candidate but emphatically refuse brain surgery, generally because of an excessive fear of potential complications; and second, patients with very severe epilepsy in whom surgery can be contemplated despite a high risk of failure and/or functional post-operative deficit. Under such conditions, it would appear legitimate to
Epilepsy

consider VNS as a sound alternative treatment, in as much as this would not rule out later surgery. Another potential indication for VNS is represented by the failure of resective surgery. A few studies suggest that these patients are less likely to respond to VNS than the general population of patients with drug-resistant partial epilepsy, 

but this issue remains controversial. 

Profiling Vagus Nerve Stimulation Responders

As a Function of the Side and Localisation of the Epileptogenic Zone

A few studies have evaluated whether the lateralisation of the epileptogenic zone (EZ) influences the efficacy of VNS, and showed only a non-significant trend towards a slightly higher rate of responders among patients with a right-sided EZ. Other small series have reported non-significant trends towards greater efficacy in patients suffering from temporal unilateral, bitemporal or frontal lobe epilepsy. Thus, at present there is no strong indication that the antiepileptic effect of VNS depends on the side or localisation of the underlying EZ.

As a Function of the Underlying Lesion

Some studies suggest that VNS is more effective in patients whose epilepsy is symptomatic of an underlying brain lesion, most notably malformation of cortical development, including tuberous sclerosis. However, this issue remains controversial, with other series showing greater efficacy of VNS in patients with non-lesional epilepsies, or comparable findings in patients with and without abnormal findings on magnetic resonance imaging (MRI).

As a Function of the Associated Co-morbidity

A significant number of patients with refractory epilepsy also suffer from depressive co-morbidity, at times promoted by AEDs. In contrast, VNS has been shown to have antidepresive properties in patients with epilepsy, regardless of its impact on seizure frequency. This finding led to the development of several VNS studies in non-epileptic patients with drug-resistant major depressive disorder, confirming the positive impact of VNS on mood disorders. In the same way, VNS allows for improvement in the quality of life and behaviour of epileptic patients, including those who do not benefit from a significant reduction in seizure frequency. All of these findings suggest that VNS might be particularly useful in the management of patients with both refractory seizures and depressive co-morbidity.

As a Function of Age

In three large paediatric trials, the 50% responder rate was found to be equal to or greater than that reported in adults, ranging from 46 to 83% after two years of follow-up. Tolerability also proved comparable to that observed in adult populations.

indications for vagus nerve stimulation in refractory generalised epilepsy

Several studies suggest that VNS is effective in drug-resistant idiopathic or symptomated generalised epilepsy. The average reduction in seizure frequency appears comparable in these types of epilepsies (around 45% for follow-up ranging from three to 21 months) to that observed in partial epilepsies, although a few studies suggest that higher responder rates could be observed in patients with symptomatic generalised epilepsy, specifically. VNS appears to be efficacious against all types of generalised seizures, including myoclonic jerks, tonic seizures, absences and generalised tonic-clonic seizures. In Lennox-Gastaut syndrome, the average reduction in seizure frequency was found to be greater for atypical absences and tonic seizures (73 and 55%, respectively) than for partial seizures (23%). However, the efficacy of VNS in Lennox-Gastaut syndrome remains a controversial issue. In childhood absence epilepsy, where about 5% of patients are drug-resistant, VNS was evaluated in a multicentric study of 16 children with a mean age of eight years. The 50% responder rate was 38% after six months of follow-up, rising to 88% at 18 months. Conversely, in infantile spasms VNS does not seem efficacious, with only two responders out of a series of 10 patients.

Vagus Nerve Stimulation versus Callosotomy

The anecdotal observation that VNS might be particularly efficacious against seizures associated with traumatic falls has led to the comparison of VNS with callosotomy in adult patients suffering from generalised seizures. The 50% responder rate for tonic and atonic seizures was comparable between the VNS and callosotomy groups (67 and 78%, respectively), while there was no non-significant trend towards a higher rate of complications in the group treated with callosotomy (21%, including 3.8% of permanent deficits) than in the VNS group (8%, with no permanent deficit). Comparable findings were recently reported in a series of 24 children suffering from Lennox-Gastaut syndrome. VNS might thus be considered an appropriate alternative to callosotomy in patients suffering from generalised seizures associated with traumatic falls.

Past or Future – Vagus Nerve Stimulation versus Deep Brain Stimulation

Several methods of deep brain stimulation (DBS) have been developed over the past 30 years using multiple brain targets such as the anterior and central median nuclei of the thalamus, the subthalamic nucleus, the caudate nucleus or even the cerebellum. The majority of studies have been carried out on small groups and have not been properly controlled, and the results are highly variable and often contradictory. For instance, the encouraging results observed with stimulation of the central median nuclei of the thalamus were not confirmed by a double-blind, randomised study. Similarly, six series on a total of 27 patients have evaluated the stimulation of the anterior nucleus of the thalamus in patients suffering from drug-resistant focal or generalised epilepsies, showing an average reduction in seizure frequency varying from 14 to 76%. A large double-blind, randomised study is currently under way, and is hoping to reach a conclusion on the true effectiveness of this type of stimulation. In any case, the potential indications of DBS in epilepsy appear similar to those of VNS. Assuming that the trials that are under way confirm the antiepileptic action of some forms of DBS, it would become essential to directly compare these techniques with VNS with a view to evaluating their respective risks and benefits.
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Risks, Side Effects and Contraindications for Vagus Nerve Stimulation

Immediate Operative and Post-operative Complications

A peri-operative complication of VNS is the occurrence of cardiac dysrythmias. According to the manufacturer’s database, in 98 out of 60,014 implantation procedures the patient developed asystole or bradycardia during implantation of the VNS.74 Detailed reports were available in seven patients,75,77 showing that asystole resulted from a complete auroiculo-ventricular block, while atrial rhythm was normal.79 This is consistent with the functional anatomy and physiology of the left vagus nerve, which primarily supplies the airo-ventricular node and has a negative chronotropic effect (while the right vagus nerve innervates the sino-atrial node). Nevertheless, the cause of this complication remains uncertain. In order to minimise the impact of this rare side effect, a systematic verification procedure in the operating room has been proposed:

- check the placement of the stimulation electrode in contact with the left vagus nerve;
- locate the branches that supply the heart in order to avoid the simultaneous stimulation of these branches and the vagus nerve;
- check the polarity of the lead and stimulator;
- ensure the absence of pooled blood or saline solution near the stimulation electrode after nerve irradiation; and
- conduct the system diagnostics in the operating theatre according to the specific pulse generator model.

A recent follow-up study of three patients who suffered bradycardia in the operating room and who were subsequently treated with VNS showed that no further abnormality of cardiac rhythm occurred during chronic stimulation.80 Thus, the occurrence of bradycardia in the operating room does not represent a definitive contraindication to starting VNS, but requires close monitoring at the time stimulation is initiated. Furthermore, recent results confirm the lack of significant changes in cardiac rhythm and blood pressure between the on and off stimulation phases in patients treated with VNS for long periods.81 On the other hand, the occurrence of unusual discomfort and, especially, unexpected falls in a patient who has been stabilised by VNS is an indication for an electrocardiogram to look for a cardiac dysrhythmia.82 Another uncommon post-operative complication is infection of the implantation site.

Sleep Apnoea Syndrome

A polysomnographic study was carried out on 16 patients before and three months after implantation of the VNS. Two patients presented with pre-operative pathological sleep apnoea and five presented after three months of treatment.83 The sleep apnoea index had further increased in 5 out of 60,014 implantation procedures the patient developed asystole or bradycardia during implantation of the VNS.74 Detailed reports were available in seven patients,75,77 showing that asystole resulted from a complete auroiculo-ventricular block, while atrial rhythm was normal.79 This is consistent with the functional anatomy and physiology of the left vagus nerve, which primarily supplies the airo-ventricular node and has a negative chronotropic effect (while the right vagus nerve innervates the sino-atrial node). Nevertheless, the cause of this complication remains uncertain. In order to minimise the impact of this rare side effect, a systematic verification procedure in the operating room has been proposed:

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Other Common Side Effects

Insertion of the VNS can cause aesthetic concerns due to the extent of the scar, notably on the neck, and of a stimulator-related skin bulge, particularly in slim people. Good surgical technique and the smaller stimulators that have recently been developed can minimise these problems. Stimulation, typically carried out using 30-second cycles every five minutes, is often associated with a hoarse voice, which decreases over time and rarely represents a significant concern for the patient. On the other hand, the impact of VNS on the upper airways can reduce respiratory capacity in patients actively engaged in sports activities, notably running. More rarely, VNS may be responsible for variable pain at the point of stimulation in the neck, requiring a reduction in stimulation by adjusting the VNS parameters.

Other Drawbacks of Vagus Nerve Stimulation

Patients receiving VNS must be informed of the delayed anti-epileptic efficacy of the procedure (typically progressing over several months), the difficulty of removing the vagal electrode and the need to replace the battery after an average period of five years.

Conclusion

VNS is an effective, though usually not curative, antiepileptic treatment aimed at patients with drug-resistant epilepsy, either partial or generalised, for which no simple medical or surgical cure can be proposed (failure of more than three AEDs, patient not eligible for surgery, patient reluctant to be operated on or patient at high risk of surgical failure or complications). VNS is of particular benefit due to its unique tolerability profile, with some advantages over AEDs (no organ toxicity, drug interaction, immunological side effects or toxicity of the central nervous system that compromise sight, cognitive functions, mood or behaviour), but also disadvantages linked to its aesthetic, vocal and respiratory consequences. Numerous unanswered questions remain relating to the mechanisms of action, identification of future responders and value of VNS above and beyond its current use as a treatment of last resort, notably in combination with new AEDs.

8. Spanaki MV, Allen LS, Mueller WM, Morris GI, Jnd, Vagus nerve stimulation therapy: 5-year or greater outcome at a


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Just like everyone else, patients with difficult-to-treat epilepsy want to enjoy their lives. However, it is incredibly important to help patients who have tried out a number of different epilepsy treatments live with little or no seizure.

VNS Therapy has been developed for both adults and children and is applied through a small device. This non-pharmaceutical treatment is an adjunctive therapy to be used with drugs, and this means that your patients’ medication intake might be reduced. In this case, it could lead to a reduction in the side effects associated with the drugs they are taking.

VNS Therapy could help your patients to experience reductions in the frequency and intensity of their seizures. Furthermore, your patients may feel improvements in terms of their mood, alertness and sense of control.

In essence, the aim of VNS Therapy is to help your patients experience increased confidence, independence and enjoyment of life.

The reality is that there are a limited number of options in dealing with difficult-to-treat epilepsy. By choosing VNS Therapy, you might well find the option that will best suit your patients.

Brief Summary of Safety Information for the VNS Therapy™ System (Epilepsy and Depression Indications) (March 2007)

1. INTRATRACHEAL USE / PAROXYSMAL EPILEPSY (Non-US) — The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epilepsy disorder is dominated by partial seizures (with or without secondary generalization) or generalized seizures that are refractory to antiepileptic medications. Dependent on the condition. The VNS Therapy System is indicated for the treatment of chronic or recurrent seizures in patients who are in a treatment-resistant or treatment-intolerant depressive episode. 2. CONTINUOUS Vagolytic Therapy — The VNS Therapy System cannot be used in patients after a bilateral or left vagal surgery. Depth — Do not use short electrodes. 3. SUBCUTANEOUS USE — For patients implanted with VNS Therapy System Diagnostic, ultrasound is not included in this contraindication. 4. CONTRAINDICATIONS Should be considered about all potential risks and adverse events discussed in the physician's manual. This document is not intended to serve as a substitute for the complete physician's manual. The safety and efficacy of the VNS Therapy System in patients with these conditions have not been established. 5. WARNINGS — DEVICE Malfunction could cause painful stimulation or direct current stimulation. Either event could result in a seizure. The枝状部分可能含有不适用的信息或需要修正的内容。