Editorial

For reprint orders, please contact: reprints@futuremedicine.com

BIOELECTRONICS IN MEDICINE

Is vagus nerve stimulation effective in the treatment of drug-resistant epilepsy?

Ann Mertens*,[1], Paul Boon[1] & Kristl Vonck[1]

[1]Department of Neurology, Ghent University Hospital, Corneel Heymanslaan 10, 9000 Gent, Belgium

*Author for correspondence: Tel.: +32 9 332 69 46; Ann.Mertens@UGent.be

First draft submitted: 8 February 2019; Accepted for publication: 13 March 2019; Published online: 24 April 2019

Epilepsy is one of the most prevalent chronic neurological conditions affecting approximately 0.5–2% of the population worldwide [1]. Patients with epilepsy repeatedly and unexpectedly experience sudden changes in behavior and or consciousness. Epileptic discharges can involve only a part of the brain, causing focal seizures, or the entire brain leading to generalized seizures. First-line treatment comprises pharmacotherapy with one or more anti-epileptic drugs. Several anti-epileptic drugs are currently available with distinct mechanisms of action and side effects. However, for an estimated third of epilepsy patients, seizures remain poorly controlled despite optimal medical management. After failure of at least two anti-epileptic drugs, patients suffer from drug-resistant epilepsy. For these patients, dedicated diagnostic workup in a specialized epilepsy center is warranted and other treatment options should be explored. The most effective treatment option for patients with refractory epilepsy is epilepsy surgery. Following a thorough presurgical evaluation, seizure freedom is obtained in approximately two thirds of patients with mesial temporal lobe epilepsy and half of patients with focal neocortical epilepsy [2]. Patients who are considered unsuitable surgery candidates should be considered for neurostimulation. Several types of neurostimulation have been developed including vagus nerve stimulation (VNS), deep brain stimulation and responsive neurostimulation. Availability may differ by region. Noninvasive neurostimulation techniques are also on the rise, aiming to avoid an invasive procedure and accompanying side effects.

Invasive VNS is a neurostimulation therapy which activates vagal nerve fibers in the neck region by means of a helical electrode that is wound around the cervical vagus nerve and is then connected with a lead to a subclavicularly implanted pulse generator. In 1997, it was approved by the US FDA as an adjunctive treatment for drug-resistant epilepsy. The mechanism of action of VNS remains to be fully elucidated. Several lines of evidence support that VNS induces a norepinephrine release in the hippocampus and cerebral cortex through the vagus nerve–locus coeruleus system leading to its seizure-suppressing effect [3,4].

The efficacy and safety of VNS have been extensively investigated by several multicenter randomized controlled trials. During the short-term follow-up of the blinded phase of the randomized trials, seizure frequency was reduced with 30% with a responder rate (proportion of patients with $\geq$50% seizure frequency reduction) of 38% [5]. In the open label extension phase, efficacy further increased to 55% seizure frequency reduction after approximately 5 years of treatment with a responder rate of 63% [6,7]. After 10 years of treatment, seizure frequency reductions of up to 75% have been reported [8]. These results lead to the current consensus on efficacy that after long-term treatment up to two thirds of patients have a considerable improvement in seizure control with a reduction in seizure frequency of at least 50%, when VNS is part of their best medical practice for drug-resistant epilepsy. In up to a third of patients little or no effect is observed on seizure frequency, but positive effects on mood and alertness may be present, irrespective of seizure control. Seizure freedom is obtained in less than 10% of patients. These results show that the individual response to VNS is variable, indicating the need for predictors to identify VNS responders before implantation, thereby avoiding the risks and costs of an unnecessary surgical procedure. Few cost–benefit data are currently available. Results show that VNS leads to a positive cost-beneficial balance mainly due to a significant reduction in hospital admissions, emergency room visits [9] and positive effects on status epilepticus occurrences [10]. The most frequently reported side effects are hoarseness and voice change during stimulation and ramping up of the therapy [6]. Outcome and side-effect profile are similar in adults and children.

Over the years, various VNS devices have been developed aiming to improve efficacy and safety. The first devices delivered stimulation in an open loop fashion with intermittent stimulation of the vagus nerve in cycles of ON

Future Medicine

and OFF periods. On top of this standard stimulation mode, the therapy also comprised a magnet feature allowing patient or caregivers to administer an additional stimulation at the time of a perceived seizure by passing the magnet across the pulse generator. Studies have demonstrated the added benefit of this magnet feature [11], but unfortunately manual use of the magnet is often challenging for patients due to seizure symptoms, nocturnal seizures or cognitive or physical impairments. To overcome this issue, a new VNS device, the AspireSR®, with a seizure detection algorithm automatically triggering stimulation has been developed. The device contains a cardiac-based seizure detection algorithm that detects ictal heart rate increases and triggers stimulation if the heart rate increase exceeds a selected threshold. The European E-36 study by Boon *et al.* and the parallel US E-37 study by Fisher *et al.* prospectively evaluated the performance and safety of this new approach. Both studies showed a high sensitivity for seizure detection with an acceptable false-positive rate. The reduction in seizure frequency was comparable to open-loop VNS, with responder rates of 30–50% and significant improvements in quality of life [11,12]. A recent retrospective study by Hamilton *et al.* showed a higher responder rate of 59% for new implantations with the AspireSR VNS system and also found improvement sooner in the course of follow-up compared with the traditional VNS devices. In addition, they found that 71% of patients with a battery change from the previous models to the AspireSR device reported an additional improvement in seizure control, indicating that this seizure detection algorithm improves the number of responders [13]. It is expected that this automatic stimulation feature will be of most benefit to patients with ictal tachycardia who are unable to use the magnet mode. However, further research will be needed to validate the additional benefit and cost efficacy of this stimulation mode.

The most recently developed VNS device, the SenTiva™ VNS system also contains the cardiac-based seizure detection algorithm as well as new programming options, aiming to make the use of the device more convenient for both physicians and patients. It has a more compact size which is particularly beneficial to the growing pediatric population considered for VNS. The device delivers novel modes of stimulation such as burst stimulation. Two small preclinical trials suggest that burst stimulation is more effective than regular stimulation, promoting further research to the anti-epileptic effect of microburst VNS in humans [14,15].

Over the last years, several noninvasive VNS devices have been developed aiming to achieve the same effects as invasive VNS but without the need for an invasive procedure. Regarding the treatment of refractory epilepsy, most research has been conducted with transcutaneous auricular VNS. This noninvasive neurostimulation modality stimulates the cutaneous receptive field of the auricular branch of the vagus nerve in the outer ear. It has been demonstrated with functional imaging studies that stimulation at this location leads to a significant activation of intracranial structures that are similarly activated by invasive VNS [16]. Only a few randomized controlled trials have been conducted showing inconsistent results and a large variability in methodology. Nevertheless, there seems to be a trend toward significant seizure frequency reduction, stimulating further research of this device and the optimal stimulation parameters [17–19]. This noninvasive approach will be attractive to many patients, although we can imagine that the lifelong use of an external device may be inconvenient. By combining these devices with an appropriate biomarker, they could however have an added value, using them as a predictor for the response to invasive VNS.

We can conclude that there is sufficient evidence demonstrating that VNS is an effective adjunctive treatment for refractory epilepsy patients not eligible for epilepsy surgery. The efficacy of VNS seems to be comparable to other neurostimulation modes such as deep brain stimulation of the anterior nucleus of the thalamus and responsive neurostimulation [20]. However, no head-to-head comparative trials have been conducted to confirm this statement. Patients considered for neurostimulation should be evaluated according to the proposed prestimulation evaluation protocol by Carrette *et al.* to decide on the appropriate type of neurostimulation [20]. The main challenge for VNS remains identifying responders before patients are implanted. The development of noninvasive VNS devices in combination with appropriate biomarkers could identify patients who would benefit from VNS therapy and is therefore gaining scientific interest.

Financial & competing interests disclosure

A Mertens is supported by an 'Aspirant' grant of the 'Fonds voor Wetenschappelijk Onderzoek' (FWO) Flanders. P Boon is supported by grants of the FWO Flanders, the Ghent University Research Fund (BOF), Ghent University Hospital and E-Epilepsy (EU). K Vonck has been funded by the BOF-UGent, special research fund from Ghent University Hospital. P Boon has received consultancy and speaker fees from UCB Pharma, LivaNova, Medtronic and Eisai. K Vonck has received speaker fees from Livanova. P Boon and K Vonck have received free devices for research studies in normal volunteers and preclinical studies from LivaNova, Cerbomed, Neurosigma and Medtronic. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1. Hauser WA, Hesdorffer DC. Epilepsy: frequency, causes and consequences. Demos Medical Publishing, NY, USA, 1–51 (1990).
2. Englot DJ, Chang EF. Rates and predictors of seizure freedom in resective epilepsy surgery: an update. *Neurosurg. Rev.* 37(3), 389–404 (2014).
3. Roosevelt RW, Smith DC, Clough RW, Jensen RA, Browning RA. Increased extracellular concentrations of norepinephrine in cortex and hippocampus following vagus nerve stimulation in the rat. *Brain Res.* 1119(1), 124–132 (2006).
4. Raedt R, Clinckers R, Mollet L *et al.* Increased hippocampal noradrenaline is a biomarker for efficacy of vagus nerve stimulation in a limbic seizure model. *J. Neurochem.* 117(3), 461–469 (2011).
5. Ben-Menachem E, Manon-Espaillat R, Ristanovic R *et al.* Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. *Epilepsia* 35(3), 616–626 (1994).
6. Morris GL 3rd, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01–E05. *Neurology* 53(8), 1731–1735 (1999).
7. Elliott RE, Morsi A, Kalhorn SP *et al.* Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. *Epilepsy Behav.* 20(1), 57–63 (2011).
8. Elliott RE, Morsi A, Tanweer O *et al.* Efficacy of vagus nerve stimulation over time: review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS > 10 years. *Epilepsy Behav.* 20(3), 478–483 (2011).
9. Boon P, Vonck K, D'Have M, O'Connor S, Vandekerckhove T, De Reuck J. Cost-benefit of vagus nerve stimulation for refractory epilepsy. *Acta Neurol. Belg.* 99(4), 275–280 (1999).
10. Shahwan A, Bailey C, Maxiner W, Harvey AS. Vagus nerve stimulation for refractory epilepsy in children: more to VNS than seizure frequency reduction. *Epilepsia* 50(5), 1220–1228 (2009).
11. Fisher RS, Afra P, Macken M *et al.* Automatic vagus nerve stimulation triggered by ictal tachycardia: clinical outcomes and device performance–The U.S. E-37 Trial. *Neuromodulation* 19(2), 188–195 (2016).
12. Boon P, Vonck K, van Rijckevorsel K *et al.* A prospective, multicenter study of cardiac-based seizure detection to activate vagus nerve stimulation. *Seizure* 32, 52–61 (2015).
13. Hamilton P, Soryal I, Dhahri P *et al.* Clinical outcomes of VNS therapy with AspireSR((R)) (including cardiac-based seizure detection) at a large complex epilepsy and surgery centre. *Seizure* 58, 120–126 (2018).
14. Martle V, Peremans K, Raedt R *et al.* Regional brain perfusion changes during standard and microburst vagus nerve stimulation in dogs. *Epilepsy Res.* 108(4), 616–622 (2014).
15. Szabo CA, Salinas FS, Papanastassiou AM *et al.* High-frequency burst vagal nerve simulation therapy in a natural primate model of genetic generalized epilepsy. *Epilepsy Res.* 138, 46–52 (2017).
16. Yakunina N, Kim SS, Nam EC. Optimization of transcutaneous vagus nerve stimulation using functional MRI. *Neuromodulation* 20(3), 290–300 (2017).
17. Rong P, Liu A, Zhang J *et al.* Transcutaneous vagus nerve stimulation for refractory epilepsy: a randomized controlled trial. *Clin. Sci. (Lond.)* doi:10.1042/CS20130518 (2014).
18. Bauer S, Baier H, Baumgartner C *et al.* Transcutaneous vagus nerve stimulation (tVNS) for treatment of drug-resistant epilepsy: a randomized, double-blind clinical trial (cMPsE02). *Brain Stimul.* 9(3), 356–363 (2016).
19. Barbella G, Cocco I, Freri E *et al.* Transcutaneous vagal nerve stimulation (t-VNS), an adjunctive treatment option for refractory epilepsy. *Seizure* 60, 115–119 (2018).
20. Carrette S, Boon P, Vonck K. A prestimulation evaluation protocol for patients with drug resistant epilepsy. *Seizure* 44, 137–142 (2017).