Epileptic Disord 2005; 7 (Suppl. 1): S22-S26

VNS Therapy *versus* the latest antiepileptic drug

Elinor Ben-Menachem[1], Jacqueline A. French[2]

[1] Department of Clinical Neuroscience, Sahlgren University Hospital, Sweden
[2] Department of Neurology, University of Pennsylvania, USA

ABSTRACT – *Pro AED:* The central issue in medical decision-making is risk-benefit assessment. Surgery of any type is still considered to be a major undertaking. To warrant these risks, the patient has a right to expect that they have a greater chance of a good outcome with an invasive therapy than with a non-invasive one. The main question is when, if ever, this becomes the case when comparing implantation of a VNS Therapy System *versus* adding an antiepileptic drug (AED)? After the first drug? The second? After all AEDs have failed? To date, no randomized trial comparing the addition of an AED against vagus nerve stimulation (VNS Therapy) has been undertaken, although several are currently being contemplated. Without this information, it is more difficult to make a case for early implementation of VNS Therapy. Unfortunately, few data are available regarding the potential for patients to become seizure-free after implantation of a VNS Therapy System. Another issue is side effects. It is important to remember that VNS Therapy also produces adverse events, albeit very different in character than those associated with AEDs, to which physicians have become accustomed. These include cough, dyspnea, pharyngitis, voice alteration and sleep apnea. A less frequently discussed, potentially negative consequence of VNS Therapy relates to the ability to obtain imaging of the patient. Patients who have undergone VNS Therapy System implantation are not candidates for imaging of the chest, breast, or abdomen. A second issue is that imaging of the brain can only be performed with MRI scanners that meet certain requirements, and as MRI technology develops, scanners meeting these requirements may become harder to find. However, to summarize, VNS Therapy is an excellent and useful treatment choice. Fortunately, the choice between AEDs and VNS Therapy is not an "either/or" decision. Each has a role in the treatment of patients with epilepsy, and the advantages and disadvantages of each should be kept in perspective.

Pro VNS Therapy: VNS Therapy is no longer a new treatment for patients with refractory epilepsy. The first implant was performed in l988, and since then more than 30,000 patients have received this therapy. It is no longer considered an unusual or dangerous procedure, but it is still used almost exclusively for refractory epilepsy patients and it has not been generally accepted for use as a first line or even second line therapy. However, compared to the new AEDs, VNS Therapy has similar efficacy results in clinical trials and in many epilepsy syndromes and the long-term efficacy results are even more positive, with continued improvement in seizure reduction for up to two years. Two of the major reasons for not using VNS Therapy early are that it is a surgical procedure, and its safety during MRI procedures, especially with 3 Tesla, has not yet been elucidated. The safety profile of VNS Therapy is very favorable; the side effects being totally different from those seen with AEDs. The most important aspects are that there have been no pharmacological interactions, cognitive or sedative side effects reported, and it is safe for use in all age groups. Side effects are restricted to local irritation, hoarseness, coughing and, in a few cases, swallow-

Correspondence:
Prof. E. Ben-Menachem, MD, PhD
Department of Clinical Neuroscience,
Sahlgren University Hospital,
413 45 Göteborg,
Sweden
Tel.: (+00 46) 31 21 22 15
Fax: (+00 46) 31 21 15 52
<elinor.ben-menachem@neuro.gu.se>

Presented at the 26th International Epilepsy Congress, Paris 2005

ing difficulties when the stimulator is on, but these tend to disappear with time. No idiosyncratic side effect has emerged during the 16 years of use. Compliance is guaranteed. The cost of the implantation of the VNS Therapy System, when spread out over 8 years (battery life), is actually less than the cost of using a new AED over an eight-year period, and real savings as regards hospital costs due to seizures can be expected.

Key words: epilepsy, vagus nerve stimulation, VNS Therapy, antiepileptic drug

Arguments in favor of VNS Therapy (Elinor Ben-Menachem)

VNS Therapy is a new treatment available for patients with refractory epilepsy. The first implantation was performed in l988, and since then more than 30,000 patients have received this therapy. There was initial skepticism among epileptologists concerning VNS Therapy, and many questioned its efficacy. Many were under the impression that VNS Therapy proponents promoted VNS Therapy implantation rather than traditional surgery when it was indicated. VNS Therapy however, compares well against AEDs with regard to efficacy and side effects, as most short-term and long-term follow-up studies have indicated (Ben-Menachem 2002a). All patients entering into earlier VNS Therapy protocols were usually extensively evaluated for epilepsy surgery before undergoing implantation with a VNS Therapy System. VNS Therapy has now been in clinical use in Europe since 1994 and in the USA since 1997, so it is no longer considered an unusual or dangerous therapy, but it is still used almost exclusively for refractory epilepsy patients and has not been generally accepted for use as a first line or even second line therapy.

Why not?

Of course it is an invasive procedure but once implanted and functioning it has very few really troublesome side effects. Indeed, there is no rational reason why it should not be considered in the early treatment of epilepsy. What are the advantages of VNS Therapy that could be envisioned for use in refractory and even in early on treatment?

1. Implantation methodology: VNS Therapy needs to be implanted. This of course is a negative aspect. It is costly too. However, once implanted the newer models of the device are primed to function for about 8 years. Spread over that period of time, the device is relatively cheap. The VNS Therapy generator is placed in the upper left chest with the stimulating lead attached to the left vagus nerve in the neck. The generator is then programmed externally with a programming wand attached to a personal computer. Frequency, output current, pulse width, signal-on time, signal-off time, and magnet parameters are adjusted by the physician using the programming system.

2. Besides the intermittent stimulation programmed in the device by the physician, there is also *a magnet* provided that can restart the programming at its own parameters for a brief time in order to try to abort an emerging seizure. Magnet parameters may be programmed to their own settings by the same method as for the continual intermittent stimulation parameter settings. The beauty of this is that when a patient experiences an aura or a simple partial seizure they can use the magnet to abort the pending seizure. In a number of studies, the magnet function seems to be useful in about 30% of patients (Morris 2003). Using the magnet helps patients develop a means to exert control over their seizures and not just stand by as an observer waiting for them to develop. After a while, the magnet response might even turn into a positive, conditioned behavior.

3. The safety profile of VNS Therapy is very favorable and the side effects are totally different from those seen with AEDs (Ben-Menachem 2002a). Cognitive and sedative side effects are not generally reported. In fact, many actually report an increase in awareness. Indeed, a preliminary study in Alzheimer patients has shown promising results; cognition being preserved for a period of 1 year (Sjögren 2002). Significant side effects are restricted to local irritation, hoarseness, coughing and in a few cases, swallowing difficulties when the stimulator was on. The good part is that all are immediately reversible with reduction of the stimulation parameters or when the generator is turned off (Ramsay *et al.* l994). VNS Therapy does not interfere negatively with concomitant AEDs or any other drug given for other disorders. No idiosyncratic side effect or pharmacodynamic interaction was ever noted in 15 years of use (Ben-Menachem 2002a). This of course is very different from AEDs. The new AEDs have been heralded as showing great promise, and everyone thought that the side effect profiles would be more favorable than those observed for older AEDs. However, there have been several surprises especially in the emergence of some, very bothersome sedative CNS and cognitive side effects, and even troubling idiosyncratic reactions.

4. The mechanism of action of VNS Therapy is unknown, but afferent projections of the vagus nerve are synaptically connected to many areas of the brain known to be involved in the initiation and propagation of seizures (Vonck 2003). There have been recent studies in humans demonstrating changes in the brain during stimulation, such as increased metabolism and blood flow seen in PET and MRI studies, as well as an increased turnover of amino acids (Vonck 2003). The stimulation of the vagus nerve that is tolerated by humans does not seem to significantly affect the unmyelinated c-fibers, which could potentially alter the autonomic functions of the vagus nerve. One idea is that VNS Therapy might stimulate the somatosensory fibers of the nerve that may cause an increase in sensory input to the brain. Thus, it could be said that the

mechanism of action of VNS Therapy is not totally clear, but this is also the case for most of the AEDs. For example, gabapentin, a rather old AED and its successor, pregabalin still have only rather vague theories behind the proposed mechanisms of action. The mechanism of action of lamotrigine has not yet been elucidated clearly nor has that of levetiracetam. There is a lot to be learned about the mechanisms of action of AEDs too, and we are only just beginning to learn how they effect the intracellular environment of neurons and glial cells.

5. Compared to the new AEDs, VNS Therapy has similar efficacy results in clinical trials (Cramer 2001), but the long-term efficacy results are even more positive. Retention after 3 to 5 years is better than for AEDs (Ben-Menachem 2002a, Koutroumanidis 2003). Unlike drugs, where efficacy declines with time, efficacy with VNS Therapy continues to improve over a period of 3 to 18 months and there have been no new emergent side effects or tolerance development over observation times of up to 8 years. VNS Therapy battery life is 5 to 8 years. Patients whose battery expired often experience an increase in seizure frequency. Until recently, with the development of better generators, the only sign that the device had stopped functioning was when the patient experienced an increase in seizure frequency or seizure severity. In this situation each patient actually served as his own control, demonstrating that the reduction in seizure frequency observed when using VNS Therapy was not a function of the regression towards the mean, or an effect of a seasonal fluctuation of seizure frequency. From the clinical trials, over 70% have elected to replace VNS Therapy, indicating that VNS Therapy was effective and not just an expensive placebo. Nowadays a battery indicator is available so that the device can be replaced before the battery expires, thereby eliminating the guessing game of when to replace it.

6. VNS Therapy has been studied in most seizure types and syndromes. Although most are case reports, larger studies have shown efficacy in Lennox-Gastaut syndrome (Aldenkamp 2002). A large patient registry also indicates that VNS Therapy might have a broad spectrum of activity, equal to those of some AEDs.

7. VNS Therapy has a mood elevating effect, which is advantageous in patients who suffer from depression as a comorbidity (Schachter 2004). In fact, VNS Therapy is now approved as a treatment for depression in the USA and Europe.

8. Compliance is an important issue in epilepsy. With VNS Therapy this is not a problem as the stimulation is given automatically around the clock. The patient does not have to think about this treatment at all.

9. VNS Therapy is safe for women and does not interact with the contraceptive pill or effect pregnancy. Actually, it is the ideal treatment for women of child-bearing potential. It does not affect hormones nor does it induce osteoporosis.

10. VNS Therapy is actually cost effective if the cost is spread over 4 to 8 years. We found huge monetary savings in hospital costs in patients treated with VNS Therapy for 18 months compared to a pre-implantation baseline (Ben-Menachem 2002b).

11. VNS Therapy has been shown to be safe in all age groups from small children to the elderly with Alzheimer's disease (Sjögren 2002). In fact, because of the cognitive sparing effect of VNS Therapy for at least 1 year, this appears to be a very appropriate treatment for the elderly.

Conclusion

VNS Therapy has demonstrated favorable efficacy and safety profiles when compared to the new AEDs in 3-month clinical trials, and actually improves seizure control with long term use. Side effects are usually mild and do not include the negative sedative and cognitive effects seen with most AEDs. Compliance is guaranteed automatically and the physician has total control over dosing and delivery. The additional use of the magnet or "therapy on demand" feature of the VNS Therapy can give patients a method with which to exert some control over their seizure situation. The cost of the implantation of the VNS Therapy, when spread out over 8 years (battery life), is actually less than the cost of using one new AEDs over an eight-year period, and real savings on hospital costs due to seizures can be expected.

Arguments in favor of AEDs (Jacqueline A. French)

Recent data from a large observational study of patients with newly diagnosed epilepsy, indicates that about 60% of patients who are newly diagnosed with epilepsy will attain control of seizures with their first or second AED (Kwan 2000). Thus, AEDs have established themselves as an effective therapy for the majority of patients with epilepsy. Yet, 30-40% of patients will fail to obtain seizure control. It is to be presumed that these patients, for the most part, will represent the population who might be considered for VNS Therapy. For these individuals, the chance of becoming seizure-free on an alternative antiepileptic drug may be as low as 11%. Adding AEDs carries the potential for increased side-effect burden. For these reasons, it might certainly be an attractive alternative to consider a device such as a VNS Therapy System.

Although both strategies carry certain advantages, for the purpose of this debate, I will discuss only the potential advantages of AEDs over VNS Therapy.

Of course, the central issue in medical decision-making is risk-benefit assessment. To most people, as noted by Prof. Ben-Menachem, surgery of any type is still considered to be a major undertaking, requiring general anesthesia, and subject to the possibility, albeit small, of significant risks such as infection and vocal cord paralysis. In addition,

repeat surgeries are necessary at infrequent intervals when the battery expires. To warrant these risks, the patient has a right to expect that they have a greater chance of a good outcome with an invasive therapy than with a non-invasive one. The main question is when, if ever, this becomes the case when comparing implantation of a VNS Therapy System against adding an AED? After the first drug? The second? After all AEDs have failed? To date, no randomized trial comparing addition of an AED against VNS Therapy has been attempted, although several are currently being contemplated. Without this information, it is difficult to make a case for an early decision for VNS Therapy.

Another issue for consideration is the potential for patients to become seizure-free after implantation of the VNS Therapy System. At least one study has demonstrated that reducing seizure frequency in patients with refractory seizures is not sufficient to improve quality of life. In this study, Health-Related Quality Of Life (HRQOL) was assessed with the Quality Of Life In Epilepsy (QOLIE)-89 survey, in 134 patients randomized to drug-*versus*-placebo as add-on therapy. Complete elimination of seizures associated with alteration of awareness was necessary to substantially improve quality of life. A 50% reduction in seizures, a commonly used endpoint in clinical trials, was insufficient to produce substantial improvement (Birbeck 2002). A recent study at the University of Pennsylvania, evaluated a population of patients with refractory epilepsy, as defined by a failure of at least two antiepileptic drugs, and occurrence of at least one seizure per month. These patients were followed for three years, and a 5% per year rate of at least six months seizure-remission was found, which was cumulative over time. In other words, over a three-year period, 15% had gone into remission, and 10.6% of this remission could be related to addition of a new antiepileptic drug (Callaghan 2004). In contrast, no patients who had implantation of a VNS Therapy System became seizure-free. Of course, it is quite likely that the patients selected for VNS Therapy System implantation had seizures that were more difficult to control than the refractory population as a whole. Some studies have reported seizure freedom for one year or more after VNS Therapy System implantation, but it is unclear whether antiepileptic drugs were also added or changed in these patients, and typically, seizure freedom did not occur immediately after implantation (Boon 1999, Janszky 2005). It is important to note, that when an antiepileptic drug is ineffective, it is often withdrawn so that another antiepileptic drug can be added. In contrast, a VNS Therapy System frequently remains in place. Therefore, it is difficult to determine whether the seizure reduction or seizure-freedom that occurs months, or even years after the implantation, is as a result of the VNS Therapy System, or in spite of it. Again, only a randomized trial comparing antiepileptic drug therapy to VNS Therapy System therapy could answer this question.

Another potential issue is side effects. Although it is clear that AEDs carry a risk of sedation, dizziness, diplopia, and other central nervous system side effects, the patient can make their own decision about whether to tolerate these risks, or to discontinue therapy and try an alternative solution. Some adverse events of VNS Therapy are reversible, including hoarseness and coughing. However, others that might be related to the implant itself may be harder to reverse. In an attempt to compare side effects of the new AEDs and VNS Therapy, Cramer *et al.* reviewed the overall rate of CNS, psychiatric/psychological and general medical side effects, with placebo subtracted (Cramer *et al.* 2001). VNS Therapy had fewer overall CNS side effects than some, but not all new AEDs. In its favor, no patients reported psychiatric/psychological side effects with VNS Therapy. However, the general medical complaint rate was over three times higher than from any AED therapy. Medical complaints included paresthesias, increased cough, dyspnea, pharyngitis, and voice alteration (hoarseness). These results are somewhat confounded, in that placebo rates were subtracted from the complaint rates for AEDs, but could not be subtracted from VNS Therapy results, since there was no placebo arm in the randomized trial (a low-dose stimulation paradigm was used). In addition, it is common for such side-effects to lessen over time. Other somatic side effects, such as sleep apnea, have also been reported, which can have clinical implications (Holmes 2003, Malow 2000). It is important to remember that VNS Therapy does, indeed produce adverse events, albeit very different in character from AED side effects to which physicians have become accustomed.

The lack of central nervous system side-effects and blood monitoring, which is often part and parcel of using antiepileptic drugs, is an attractive aspect of VNS Therapy. However, there are very few data on using VNS Therapy as "monotherapy". In fact, patients reported as seizure-free in several series were still receiving as many as three antiepileptic drugs, in addition to their VNS Therapy System (Boon 1999). This may be partially due to a fear on the part of the treating physician that the patient could be destabilized with AED withdrawal. In fact, it is quite rare that patients have all of their antiepileptic drugs withdrawn. Therefore, it is difficult to say whether these types of advantages can truly be realized in most patients.

A less frequently discussed, potential negative consequence of implantation of a VNS Therapy System relates to the ability to obtain imaging of the patients when necessary. Although this may appear to be a minor issue, in actual fact it may result in major consequences that cannot be anticipated when the implantation is performed. Potential neuroimaging consequences of VNS Therapy System implantation are of three types. The first relates to body imaging. Patients with VNS Therapy System implantation

are no longer candidates for imaging of the chest, breast, or abdomen (Benbadis 2001). Although the individual may be quite healthy when the stimulator is implanted, there is no guarantee that other illnesses might not occur that would require such imaging. Physicians may find themselves in a situation where body imaging would be the optimal way to rule out a problem, but the quality of the imaging is low. In that case, it would be very difficult to decide whether to put the patient through the removal of their device, possibly, for no gain. A second, perhaps more problematic issue is that imaging of the brain can only be performed on MRI scanners that meet certain requirements. If physicians prefer to undertake scanning on MRI machines that do not meet these requirements (which included scanners of higher sophistication, above 1.5 Tesla), the wire coil around the vagus nerve may need to be removed. This procedure is associated with risk of damage of the vagus nerve. Also, it is not entirely clear that 1.5 Tesla and below, MRI scanners will remain available when higher Tesla magnets become state-of-the-art.

In summary, VNS Therapy is an excellent and useful therapy. Fortunately, the choice between AEDs and VNS Therapy is not an "either/or" decision. Each has a role in the treatment of patients with epilepsy, and the advantages and disadvantages of each should be kept in perspective. □

References

Aldenkamp AP, Majoie HJ, Berfelo MW, *et al.* Long-term effects of 24-month treatment with vagus nerve stimulation on behaviour in children with Lennox-Gastaut syndrome. *Epilepsy Behav* 2002; 5: 475-9.

Benbadis SR, Nyhenhuis J, Tatum WO, *et al.* MRI of the brain is safe in patients implanted with the VNS Therapy System. *Seizure* 2001; 10: 512-5.

Ben-Menachem E, Hellstrom K, Verstappen D. Analysis of direct hospital costs before and 18 months after treatment with vagus nerve stimulation therapy in 43 patients. *Neurology* 2002; 59(Suppl 4): S44-S47.

Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. *Lancet Neurol* 2002; 1: 477-82.

Birbeck GL, Hays RD, Cui X, Vickrey BG. Seizure reduction and quality of life improvements in people with epilepsy. *Epilepsia* 2002; 43: 535-8.

Boon P, Vonck K, Vandekerckhove T, *et al.* Vagus Nerve Stimulation for Medically Refractory Epilepsy; Efficacy and Cost-Benefit Analysis. *Acta Neurochir (Wien)* 1999; 141: 447-53.

Callaghan BC, French JA, Anand K, *et al.* Treatment Changes Associated With Remission in a Refractory Adult Epilepsy Population. *Epilepsia* 2004; (abstract).

Cramer J, Ben Menachem E, French JA. Review of treatment options for refractory epilepsy: new medications and vagus nerve stimulation. *Epilepsy Res* 2001; 47: 17-25.

Cramer J, Ben-Menachem E, French J. Treatment options for refractory epilepsy: new medications and vagus nerve stimulation. *Epilepsy Res* 2001; 47: 17-25.

Holmes MD, Chang M, Kapur V. Sleep apnea and excessive daytime somnolence induced by vagus nerve stimulation. *Neurology* 2003; 61: 1126-9.

Janszky J, Hoppe M, Behne F, *et al.* Vagus nerve stimulation: predictors of seizure freedom. *J Neurol Neurosurg Psychiatry* 2005; 76: 384-9.

Koutroumanidis M, Binnie CD, Hennessy MJ, *et al.* VNS Therapy in patients with previous unsuccessful resective epilepsy surgery: antiepileptic and psychotropic. *Acta Neurol Scand* 2003; 107: 117-21.

Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000; 342: 314-9.

Malow B, Edwards J, Marzec M, *et al.* Effects of vagus nerve stimulation on respiration during sleep: a pilot study. *Neurology* 2000; 55: 1450-4.

Morris 3rd GL. A retrospective analysis of the effects of magnet-activated stimulation in conjunction with vagus nerve stimulation therapy. *Epilepsy Behav* 2003; 6: 740-5.

Ramsay RE, Uthman BM, Augustinsson LE, *et al.* First International Vagus Nerve Stimulation Study Group. Vagus Nerve Stimulation for Treatment of Partial Seizures: 2. Safety, Side Effects, and Tolerability. *Epilepsia* 1994; 35: 627-36.

Schachter SC. Vagus nerve stimulation: mood and cognitive effects. *Epilepsy Behav* 2004 (Suppl 1): S56-S59.

Sjögren M, Hellström P, Johansson M, *et al.* Cognition-enhancing effect of vagus nerve stimulation in patients with Alzheimer's disease - a pilot study. *J Clin Psychiatry* 2002; 63: 972-80.

Vonck K, Boon P, Goossens L, *et al.* Neurostimulation for refractory epilepsy. *Acta Neurol Belg* 2003; 4: 213-7.