Vagus Nerve Stimulation (VNS) for Treatment-Resistant Depression

Summary

✓ Vagus nerve stimulation, originally used to reduce seizures in epilepsy patients, is now under investigation for treatment-resistant depression.

✓ A device used for vagus nerve stimulation, the NeuroCybernetic Prosthesis (NCP®) System, recently received Health Canada approval for use in treatment-resistant depression. It is still considered to be an "investigational" device for this purpose by the U.S. Food and Drug Administration.

✓ Only the results of a small, uncontrolled study have as yet been published in full. Results of a randomized, multi-centre trial should be available early in 2002.

✓ It is not yet clear which patients with major depression will respond to vagus nerve stimulation therapy and whether those who do so will sustain their response.

✓ The cost of the device and the disposable equipment used for implantation are estimated at C $15,000. Surgical and follow-up costs will incur additional expenses.

The Technology

Vagus nerve stimulation (VNS) is a general term that encompasses different methods used to stimulate the vagus nerve. It has been used for several years in epilepsy patients whose seizures could not be adequately controlled with medication. Researchers noticed that some of the patients receiving VNS experienced an improvement in mood. However, the exact mechanisms by which VNS affects the brain are not yet understood.

The VNS device consists of a small generator (similar to a cardiac pacemaker) that is surgically implanted into the upper, left wall of the chest. A bipolar lead is wrapped around the left vagus nerve through a separate incision in the neck. The lead is tunneled underneath the skin and connected to the generator. The surgical procedure takes about an hour and is performed under general anaesthetic. Many physicians prefer to keep their patients in hospital overnight for observation following the surgery (XYCORP Medical Inc., 2001 Aug 20: personal communication). The physician programs the unit to deliver an intermittent electrical current to the left vagus nerve. The starting level for stimulation suggested by the manufacturer is 30 seconds on and five minutes off, with adjustments as needed. There does not appear to be a correlation between the intensity of the stimulation and the efficacy of the treatment (XYCORP Medical Inc., 2001 Oct 4: personal communication). The battery life of the most recent model of the generator is estimated as 8-12 years, but this will depend on the level and frequency of electrical stimulation used. Replacing the generator requires another surgical procedure.

Regulatory Status

The NeuroCybernetic Prosthesis or NCP® System (Cyberonics Inc., Houston, TX) is currently the only commercial device available for VNS. It was originally approved in Canada and the U.S. in 1997, for the reduction of seizures due to refractory epilepsy. In April 2001, Health Canada expanded licensing of the device to include a new indication for "the treatment of chronic or recurrent depression in patients that are in a treatment resistant or treatment intolerant major depressive episode." The device has been available in Europe since 1994 for the treatment of epilepsy and received the European CE mark of approval for treatment of major depressive disorder and Bipolar I and II disorder in March 2001. The U.S. Food and Drug Administration considers the use of the NCP® System in depression to be "investigational".

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is a non-profit organization funded by the federal, provincial and territorial governments. (www.ccohta.ca)
Recent data from the National Population Health Survey indicates that about one million Canadians may have an episode of major depression each year. Approximately 10% of these episodes may be considered chronic. However, depression is often either not recognized or not properly treated. Consequently, not all those who experience chronic or recurrent depression are actually treatment-resistant. VNS may be an option for some patients who have not responded to adequate treatment with standard therapies. As yet, there are no formal guidelines for patient selection or the use of this device in the treatment of depression (XYCORP Medical Inc., 2001 Oct 4: personal communication).

Many therapies are available for the treatment of major depression. Therapy usually begins with a single course of an antidepressant drug. For patients who do not respond after several weeks the dosage may be increased, or the patient may be switched to a different type of antidepressant. Combinations of antidepressant and antipsychotic medications, psychotherapy and electroconvulsive therapy may also be used. Several clinical practice guidelines outline current recommendations for the treatment of major depression.

The costs of the generator, lead and disposable tunneling tool used for implantation are about $15,000. There are additional health care costs associated with the surgery and follow-up. The cost of the device and the implantation surgery in the U.S. has been estimated at $25,000.

The economic and social burden of depression is considerable. A study sponsored by Cyberonics found that treatment resistance was associated with increased hospitalization, increased use of outpatient services, and two to three times more psychotropic drug use, in addition to antidepressant medications, when compared to non-treatment-resistant patients treated for depression. Studies of the costs of depression often underestimate the burden of disease by failing to include indirect costs, such as the impact on health service utilization and the burden of depression on family members.

Upon approval in the U.S., Cyberonics plans to conduct intensive direct-to-consumer marketing of the NCP® System. The Canadian distributor and Cyberonics estimate that the market for the device for treatment of depression is at least five times that for epilepsy. To date, several hundred Canadian patients have received the NCP® System for epilepsy and three Canadians have been implanted with the device within the multicentre trial for depression (XYCORP Medical Inc., 2001 Aug 21: personal communication).

Vagus nerve stimulation using the NCP® System is also being studied for additional indications, such as, the treatment of obesity (bilateral diaphragmatic VNS), anxiety disorders, chronic migraine and Alzheimer's disease.

Several other procedures are under investigation for treatment-resistant depression. These include repetitive transcranial magnetic stimulation (rTMS), in which a magnetic field is used to create electrical currents in the left prefrontal cortex of the brain, and deep brain stimulation (stimulation of the brain with an electrode), currently used in some Parkinson's disease patients.

Only initial results from a pilot, uncontrolled study of VNS in depression (the D-01 trial) have been published. These preliminary results involved 30 adult outpatients diagnosed with major depressive disorder or bipolar I or II disorder (manic depression), who were currently in a major depressive episode of two years or more, or who had experienced four or more such episodes in the past.

All patients were implanted with the NCP® System and received 10 weeks of VNS. Patients continued on their existing medication throughout the study though increases in dosages were not allowed. Patients were allowed to continue with VNS treatment after the trial, and 29 of the 30 patients did so.

Treatment response was defined as a greater than or equal to 50% reduction in the baseline Hamilton Depression Rating Scale. Twelve of the
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Thirty patients (40%) were considered responders. The authors caution that these trial results should be considered "preliminary" due to the small sample size and the lack of blinding of the psychiatric assessments. As there was no control group, the possibility of a placebo effect or spontaneous improvement must be considered. As Andrews notes, the response rate to placebo in treatments for depression is unusually high, both because of the placebo effect of receiving treatment, and through improvement due to the natural course of the condition. However, no patients responded during the two-week, post-surgery, recovery period (before electrical stimulation began). Ten of the twelve patients who did respond to VNS, and for whom follow-up data are available, appear to have maintained their response during a follow-up period of four to nine months.

Further results from all 60 patients in the D-01 trial are described in a Cyberonics' press release, but have not yet been published in full. The preliminary results indicate that over 30% of patients showed an improvement in depressive symptoms with VNS. Again, it is possible that some level of placebo effect may be present in these results.

A 12-week, double blind, randomized, multi-centre study (the D-02 trial) of the NCP® System versus sham (delayed) VNS in 240 patients with depression is in progress. In this trial, all patients will receive the NCP® implant, but only half will have the device activated during the first 10 weeks after implantation. The results of this trial should be available early in 2002 (XYCORP Medical Inc., 2001 Aug 16: personal communication).

**Implementation Issues**

This is an expensive technology, and one that involves invasive surgery. Limited, non-controlled evidence shows some promise for a subgroup of patients with treatment-resistant depression. However, it is not known which patients will benefit from VNS or where this treatment might fit within the current treatment algorithms for recurrent depression. Whether non-responders will eventually respond with longer term VNS and whether initial responders will maintain their response are also not known. The impact of VNS on patients' use of antidepressants and other medications has not been determined. Physicians need special training to perform the implantation surgery and reports of adverse effects associated with the procedure suggest that a learning curve should be expected. Moreover, the costs and safety of surgical removal of the implants in non-responders or patients who wish to discontinue VNS treatment have not been determined.

**Adverse Effects**

The adverse effects reported by both patients with epilepsy and patients with depression, who were implanted with the NCP® System, were similar. These include hoarseness, cough or throat discomfort when the actual stimulation is taking place. Other adverse effects include headache, shortness of breath, difficulty in swallowing, indigestion, nausea, general pain and neck pain. Reported surgery-related adverse effects include: wound infection, nerve paralysys, hypesthesia (decreased sensitivity to touch), facial paresis (partial paralysis), left vocal cord paralysis, left facial paralysis, left hemidiaphragm paralysis, left recurrent laryngeal nerve injury, urinary retention and low grade fever.

The U.S. Food and Drug Administration recently amended labelling for the NeuroCybernetic Prosthesis (NCP®) System with precautions for specific conditions such as pre-existing obstructive sleep apnea and exposure to other therapies or situations involving electric current such as TENS devices, and some imaging treatments. Further contraindications and cautions are listed on the manufacturer's web site.

**References**


