

UNIVERSITY OF NEW SOUTH WALES
SOUTH-EASTERN SYDNEY AREA HEALTH SERVICE - EASTERN
SECTION

THE PRINCE OF WALES HOSPITAL

VAGUS NERVE STIMULATION FOR THE TREATMENT OF
RESISTANT DEPRESSION: AN OPEN STUDY

PATIENT INFORMATION STATEMENT

You are invited to participate in a research study to determine the effectiveness of Vagus Nerve Stimulation (VNS) as a treatment for Resistant Depression. You are considered a potential subject for this study because you have been diagnosed to suffer from Major Depression, which has persisted for over two years without a sustained period of recovery. You have also tried the available treatments for Depression and have found them to be ineffective. You also have a history of Depression in the past. If you agree to participate in this Study, you will be assessed for suitability by a Research Psychiatrist and, if considered suitable, be included in the Study. You must read this Statement carefully in order to understand the potential risks and benefits associated with this treatment.

What is VNS?

VNS refers to the long-term, intermittent stimulation of the left Vagus Nerve by a commercially available device (the NeuroCybernetic Prosthesis NCP). This is a pocket watch-sized electric signal generator which, like a cardiac pacemaker, is implanted in the chest wall on the left side. A lead wire from the device is wound round the left Vagus Nerve, and current is intermittently delivered to the nerve. The stimulation occurs automatically at set intervals, during waking and sleep. Stimuli are fast-frequency, brief pulses of alternating polarity, which are delivered in pulse trains, with pauses between trains. Stimulation parameters are programmed within a range of values that are known not to cause nerve injury based on animal experiments. Programming is performed by a medical professional using a laptop computer and magnetic transducer (wand) placed over the implanted generator. In addition, the patient can trigger a single train of stimuli by placing a hand-held magnet over the generator, and then removing the magnet. The patient can stop all stimulation for as long as he or she wishes by holding or taping the magnet over the generator.

Why the Vagus Nerve?

The Vagus Nerve is the 10th cranial nerve, which is a large bundle of nerve fibers that connects the brain to visceral organs such as the heart, lungs and the gastrointestinal tract. It carries nerve impulses from the brain to control the heart rate and the gastric tone. It also carries a large amount of information from the body organs to the brain. This information is then conveyed to diverse brain regions, and has an impact on the activity in the limbic brain, the part of the brain that controls emotion. Stimulation of the Vagus Nerve can therefore influence brain function in subtle but significant ways. It has been known for some time that such stimulation can control epilepsy. Worldwide, over 9000 patients have been treated with VNS for epilepsy. It has been observed that many of these patients sustain an improvement

in their mood. More recent studies have shown that such stimulation can help depression as well.

What is the evidence so far that VNS helps depression?

One study published in 2000 (Rush et al, 2000) reported the results of a multi-centre study from the United States which included 30 patients with Depression who had not responded to medication. In the 10 weeks of stimulation, 40% of patients showed a good response (i.e. a >50% reduction in their symptoms). These patients were followed up for a further 9 months, and it was found that 46% (13/28) had improved and 29% (8/28) were completely well (Marangall et al, 2000). This was of course an open study, and placebo-controlled studies will be necessary in the future. However, the results are sufficiently encouraging for us to pursue this treatment in Australia through an open study.

What does participation in this study involve?

Your psychiatrist must refer you to the study. You will initially be assessed for suitability, and if considered suitable, you will undergo a detailed medical and psychiatric assessment. A number of rating scales to rate your mood and general health will be administered, and a brief neuropsychological assessment done. The interview with the study psychiatrist will be videotaped for later review. You will then come into hospital for a day (and possibly one night) to receive the implantation of the stimulator. You will be followed up weekly for six weeks and then fortnightly for another 6 weeks and quarterly thereafter as long as the stimulator is in place and activated. The device will be monitored throughout, and will need programming at various stages, which will be done by one member of the research team. All assessments will be carried out at the Prince of Wales Hospital in Randwick NSW.

What will it cost you (the participant)?

Since this study is not funded by any commercial agency, you are required to pay for the NCP device. The cost for this is about \$14,000, but a discount of about 20% will be available from the company marketing it. The device has, in the past, been partially covered by Private Health Funds for the treatment of epilepsy. However, we are not certain if they would do the same for Depression, and we suggest that you contact your Health Fund if you are a member. The research team will assist you in making an application to the health fund for assistance in the purchase of the device. At present we do not have funding for the purchase of these devices, but this may change in the future. All costs of assessments will be borne by the research team. You will be required to visit the hospital at the required intervals at your own cost.

How is the device placed?

The NCP device is implanted with the patient under general anaesthesia. A subcutaneous pocket is created in the anterior chest wall below the left clavicle, and the device placed in it. The lead wires have coiled tips that are arranged around the nerve. It can be performed as a day-only procedure, but sometimes an overnight stay in the hospital may be necessary. The implantation is done by a neurosurgeon (Dr Marianne Vonau or her colleague).

What are the potential adverse effects of VNS?

Adverse effects may be related to the implantation, the stimulation of the device, or the effect on depression:

Implantation: complications of VNS using the NCP system implantation are rarely severe or persistent. Paralysis of one vocal cord occurs in approximately 1% of implantations, and fully recovers over several weeks in most cases. This results in some hoarseness of voice. Weakness of lower

facial muscles occurs in 1% of cases, and also recovers over several weeks. Fluid can accumulate at the site of implantation, with possible secondary infection, in 1-2% cases, and this responds to aspiration and antibiotics. In the published Depression study, 9 (30%) patients reported some pain at the site of the implant. Rarely, the device must be displaced because of infection that does not respond to medical therapy. Our neurosurgeon is very experienced in implanting such devices in epilepsy patients.

Stimulation: Adverse effects of electrical stimulation of the Vagus Nerve are usually mild or absent when the parameters are appropriately programmed. They occur only when the stimulation is on. Essentially, all patients will experience a tingling, or similar sensation, over the left side of the neck when the trains of pulses are delivered. These are mild and can generally be easily ignored. This sensation is worse in people who smoke. Many patients experience mild hoarseness (60%) or other vocal alteration when the trains of electrical pulses are being delivered. Intelligible speech is not prevented when the parameters are appropriately adjusted. Some patients, however, shut off the stimulator during delivery of a public presentation. Some patients experience a desire to cough during the stimulation, and are usually able to inhibit the coughing. Another experience can be a sensation of heavy or forced breathing (23%). This is mild and not associated with measurable changes in pulmonary function from one study. Other possible side effects are indigestion, vomiting, and swallowing difficulties. If you already have swallowing difficulties, this treatment may not be appropriate. If you have cardiac abnormalities, there is a potential of these being worsened by the stimulation.

In summary, while there are a number of side effects, overall these are tolerated by the patient. In the 1 year depression study, only 1 patient requested displacement of the device at 11 months because of lack of efficacy, and none because of side effects.

Depression-related: In the previously published trial, one patient developed hypomania while on VNS, a well-recognized side effect of anti-depressant treatment. Two (in 30 patients) events of agitation were reported.

Below is a complete list of adverse events that have been reported. It is important to remember that many of these adverse events can occur with any minor surgery and with depression, and are not directly a consequence of VNS itself.

Potential Surgery-Related Risks:

Adverse reaction to anesthesia	Incision pain
Blood clot	Infection
Cyst formation	Inflammation/edema
Death	Localized surgery-related pain
Device protrusion through skin	Nausea
Facial numbness	Pain
Facial paralysis	Paresthesia
Fluid accumulation	Scarring
Hematoma	Skin irritation
Histotoxic reaction	Surgery-related complications such as
suture pulls	
Hoarseness	Tissue reaction
Hypertonia	Wound healing difficulties

Potential Device & Stimulation-Related Risks:

Asthma, bronchitis	Hypertonia
Aspiration pneumonia	Hypesthesie
Agitation/anxiety/panic	Increased coughing
Cardiovascular effects, including asystole and bradycardia	Laryngismus
Device migration symptoms	Mania, hypomania, and related
Dizziness	Muscle twitching during stimulation
Dyspepsia	Nausea and vomiting
Dysphagia	Pain
Dyspnea	Paresthesia
Ear pain	Pharyngitis
Esophagitis	Seizures
Facial paresis or paralysis	Sleep disturbances/difficulties
Headache	Tinnitus
Hemidiaphragm paralysis	Tooth pain
Hiccuping	Voice alteration
Hoarseness	

Potential AEs (possible but not reported in clinical studies):

Duodenal ulcer or gastric ulcer Implant-related cerebral vascular event

Potential Depression-Related Adverse Events (possible but not reported in clinical studies):

Change in appetite/weight
 Concentration difficulties
 Depersonalization and derealization
 Feelings of guilt
 Helplessness/hopelessness/worthlessness
 Hypochondriasis
 Lethargy/fatigue/loss of energy/feeling heavy
 Obsessive and compulsive symptoms
 Paranoid symptoms
 Rejection sensitivity
 Suicide/suicidal intention or attempt

Precautions:

Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. They should not manipulate the device, as the lead may be damaged, which could cause damage to the nerve. If they go for any therapeutic procedure, they should inform the doctor and the technician about the presence of the pulse generator. This is particularly true for procedures such as mammography, X-ray examination, ultrasound therapy and MRI. While MRI scans can be performed under certain conditions while carrying a stimulator, this decision is best left to an expert.

Further questions:

If you have further questions, you can contact either

- Prof Perminder Sachdev on tel 02-93823763 or fax 02-93823774 or email p.sachdev@unsw.edu.au , or
- Dr Gin Malhi on tel 02-93823719 or email g.malhi@unsw.edu.au, or
- Dr Julian Trollor on tel 02-93823763 or email j.trollor@unsw.edu.au

This study has been approved by the Ethics Committee of the Southeastern Sydney Area Health - Eastern Section. If you have any concerns, questions or comments, please contact the Ethics Secretariat at the Prince of Wales Hospital (Ms Kim Breheny Tel: 9382 3583 Fax: 9382 2813)