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Vagus Nerve Stimulation for Refractory Epilepsy

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This Health Technology Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion and attempts to be current to the date of publication. It has been externally reviewed. Additional information and comments relative to the brief are welcome and should be sent to:

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SUMMARY

Vagus nerve stimulation (VNS) has been developed and used to improve seizure control in patients with refractory epilepsy for whom treatment options are poor. The evidence from published research suggests that VNS is safe and effective when added to the existing treatment regimen for some patients (>12 years) in terms of reduction in frequency of partial-onset seizures. Limited follow-up evidence reported by uncontrolled studies suggests a continuous decrease in seizure frequency with long-term use of VNS therapy. It appears that its benefits and safety do not diminish over time for those who continue to use it.

However, further research is still needed to determine:

- the mode of action of VNS,
- which patients are likely to respond,
- the effect of VNS in less severely afflicted patients,
- the effect of VNS in different syndromes of epilepsy,
- quality of life of treated patients and their caregivers, and
- the details of stimulation paradigms such as different stimulation protocols.

Patients considering VNS therapy and their caregivers should be aware that:

- VNS therapy appears to have a moderate initial efficacy that may increase over time but it is not a cure for epilepsy.
- VNS only should be used as a last resort only after an extensive and thorough patient evaluation to rule out non-epileptic conditions and exclude patients who may benefit from available anti-epilepsy drug therapy and epilepsy surgery.
- VNS does not work for everyone.
- The safety and efficacy of VNS in children with refractory epilepsy has yet to be established.
- VNS appears to have a favorable safety profile when compared to conventional therapies but the possibility of unknown adverse effects associated with its use still exists.

Interest in and provision of VNS therapy has increased across Canada. Eleven of the twelve Ministries of Health responding to the survey cover this procedure and the device through their medical insurance programs, and hospital budgets. The procedure is available in seven provinces, while three provinces and one territory provide coverage for the procedure to be done in another province.

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INTRODUCTION

A Technote completed by the Health Technology Assessment Unit of Alberta Heritage Foundation for Medical Research in November 1998 assessed the use of vagus nerve stimulation (VNS) for refractory epilepsy. The Technote concluded that VNS is promising but its role in epilepsy management was yet to be established. Following the completion of that report, there were new information and publications on the use of VNS for this indication. Given the growing interest in the use of VNS and the debate regarding its funding in Alberta, an update on VNS for this indication has been undertaken.

SCOPE OF THE REPORT

This report has been produced in response to a request from Alberta Health and Wellness for an update on the use of VNS for refractory epilepsy. The intent was to inform health policy makers, medical practitioners, and the public on the current status of the use of VNS for refractory epilepsy in both adults and children and on its use and coverage in Canada. This review is confined to the use of VNS therapy for refractory epilepsy.

The Technote produced by the HTA Unit in November 1998 [7] has been used as background material for this assessment. It reviewed the literature that reported on the efficacy and safety of VNS as a treatment option for patients with refractory epilepsy. The literature review was supplemented by opinion from Canadian specialists in neurology with expertise in the use of VNS therapy. The focus of the present review has been on the studies/assessments published since the completion of the Technote.

This report consists of two main sections. The first section summarizes the findings of the current review of the published literature that has provided evidence on the long-term safety and efficacy/effectiveness of VNS when used for this indication and on the issues related to its use.

The second section presents updated information on the use and coverage of VNS procedure in Canada. This information was obtained by a survey of the provincial/territorial Medical Directors across Health Ministries in Canada conducted to determine the use and provision of VNS therapy in Canada and whether the surgical procedures and devices associated with it were publicly funded/covered. This section also presents information on the commercially available VNS devices and the costs of these devices and of each of their components.

The methodological approaches used for this report are outlined in Appendices A and B. Some discussion on the costs and cost issues associated with the use of VNS for this indication is included in Appendix C.

SECTION 1

BACKGROUND

Epilepsy is a condition characterized by sudden, brief changes in how the brain works. The term is used to describe a group of syndromes characterized by the tendency to have seizures (spontaneous disturbances in the normal electrical activity of the brain, associated with changes in behavior) that have many causes and affect patients differently. Primary generalized, partial and unclassified seizures are the main types of seizures [7, 10]. They have different basic mechanisms and require different diagnostic approaches and therapies. It has been estimated that the cause of epilepsy in 75% of children and 50% of adults with the condition is unknown (http://www.epilepsy.ca/eng/mainSet.html).

Epilepsy affects about 300,000 Canadians (~1% of population), people who take anti-epileptic drugs (AEDs) or who have had a seizure within the past 5 years (http://www.epilepsy.ca/eng/mainSet.html). Each year one in 1,000 Canadians is diagnosed with epilepsy - an average of 14,000 new cases every year. About 60% of new patients are young children and elderly people.

Refractory epilepsy

The focus of epilepsy management approaches is to help the patients restore their "ability to function whether at school, at work or in society" [30]. For the majority of patients, seizures are controlled with anti-epileptic drugs (AEDs), given either singly or in combination, which may be withdrawn when the patient has been seizure-free for 2 years [10]. However, AEDs are not always a cure and can have numerous, sometimes severe, side effects (http://www.epilepsy.ca/eng/mainSet.html).

Despite the available medical therapy with AEDs, between 20% and 40% of people with epilepsy continue to experience seizures [1, 7, 10, 19]. These patients are referred to as patients with refractory or intractable epilepsy. For patients with focal onset epilepsy surgery can be an important treatment option [7, 12] (http://www.epilepsy.ca/eng/mainSet.html). However, up to 40% of patients with refractory epilepsy are not suitable candidates for epilepsy surgery [7]. Even after epilepsy surgery has been performed, there remains a group of about 10% of patients in whom seizure control cannot be achieved or is attainable at the expense of severe adverse effect [7].

In patients with refractory epilepsy, seizure frequency has been associated with reduced quality of life (QOL), increased injuries, and excessive mortality compared to age-matched individuals [7, 35]. Persistent epileptic seizures have psychological, behavioral, and cognitive consequences [10, 16] (http://www.efa.org/epusa/divide.html). Sudden unexpected death in epilepsy (SUDEP), which has been identified as a contributor to excess of mortality in patients with refractory epilepsy, is more common in these individuals (about

1/200 patients per year) [7, 19]. Larner and Farmer [19] suggest that a proportion of cases of SUDEP may "be preventable with improved seizure control".

Recently, new options for treatment of refractory epilepsy have been developed to improve seizure control in these patients including new AEDs and vagus nerve stimulation (VNS).

VNS therapy: description

The device used in clinical research on the efficacy of VNS therapy is the fully implantable NeuroCybernetic Prosthesis (NCP®) System manufactured by Cyberonics, Inc. (Texas, USA). It consists of a pulse generator (a small pacemaker-like device) which is implanted in the upper left chest and connected to a bipolar lead attached to the left vagus nerve through a wire tunneled under the skin to the lower neck.

The generator (also known as "epilepsy pacemaker") delivers intermittent electrical stimulation to the left vagus nerve in the neck with the aim of reducing seizure frequency and severity. Its parameters are set/reset externally by the physician using a programming wand attached to a standard personal computer (with accompanying NCP software). In addition to the programmed stimulation, patients and caregivers may use a magnet to activate or deactivate the system on demand by passing or holding it over the area of the chest where the generator is implanted.

The implantation of the system is accomplished during a 45-minute to 2-hour surgical procedure under general or localized anesthesia [1, 7, 8, 12]. At some centers the surgical procedure is performed on an outpatient basis but most centers admit patients for an overnight stay after implantation.

All of the stimulation parameters (current intensity, pulse width and frequency, on/off cycles) are adjustable and can be individualized based on patient's tolerance. Although the optimal parameters are yet to be determined [7], the "standard practice" is to give a stimulus (1.0-2.0 mA; 0.5 ms; 20-30Hz) in on/off cycles of 30s every 5-10 minutes, 24 hours a day [6-8, 12].

The generator is powered by a battery that must be replaced every 3 to 5 years, depending on the settings used for the stimulation parameters [1, 7, 8]. In the most recent models of VNS devices the battery may last up to 12 years (see Table 2) [8]. After battery depletion the pulse generator can be replaced under local anesthesia in an outpatient procedure within 30 to 60 minutes [1, 7].

Although the groundwork for VNS was laid about 60 years ago, the exact mechanism by which it works to control seizures is not clearly understood yet [1, 7, 12, 13].

VNS therapy: regulatory status and clinical use

VNS is a relatively new therapy that has been shown to help some people with refractory epilepsy more effectively manage their disease by reducing frequency of partial-onset seizures. It has been proposed as an adjunctive therapy to existing AED therapies. Its suggested role is to improve seizure control in terms of reduced seizure frequency in patients who have failed medical therapy, are unable to tolerate medication, are unsuitable candidates for epilepsy surgery or do not improve after surgery [7, 10, 12]. Most patients receiving VNS therapy continue medical therapy with one or more AEDs.

Since 1988, when the first NCP® system was implanted to treat human refractory epilepsy [7], the VNS has been approved as a clinical procedure for this indication in many countries. The NCP® system has received regulatory approval in the European Union countries in 1994, and in USA and Canada in 1997. It also received regulatory approval in Australia and other markets. The NCP® system has been approved for use as an adjunctive therapy (in conjunction with AED therapy or surgery) to reduce partial seizures in adolescent and adult patients (aged >12 years) with refractory epilepsy [7, 12]. The clearance of the device does not extend to treatment of primarily generalized seizures.

To date, in most cases VNS has been used to treat adolescents and adults with refractory epilepsy dominated by complex partial seizures (>6 seizures per month) although secondary generalized seizures were not excluded. However, devices have already been implanted in children younger than 12 years of age and used to treat patients with other than complex partial seizures (such as epileptic encephalopathy, absence seizures, Lennox-Gastaut Syndrome, idiopathic seizures, and primary generalized seizures) [1, 7, 12, 13, 37].

Currently there are no criteria developed to select patients who are more likely to benefit from VNS therapy and there is no method to determine whether or how well and quickly a patient may respond to it [1, 7, 8, 12, 13].

The VNS device cannot be used in patients who had a bilateral or left cervical vagotomy [1, 12]. VNS is not considered in people who suffer from cardiac, respiratory, or gastrointestinal problems, or where the effects of the implant on the voice may be troublesome (such as singers or teachers) [1, 7, 12]. Other contraindications include progressing neurological or systemic disease and pregnancy. Most clinical trials on antiepileptic pharmaceutical therapies and on use of VNS exclude patients over 65 years of age.

Since its commercial approval many insurance companies have agreed to pay hospitals in the United States to treat over 2,000 patients with VNS [8, 13, 33]. In 1998, the Health Care Financing Administration (HCFA) announced a national coverage policy to cover VNS for patients with medically refractory partial-onset seizures for whom surgery is not recommended or failed [12].

According to ECRI, VNS therapy is still in the early stages of its diffusion [12]. To date, more than 6,500 epilepsy patients in 24 countries have accumulated over 6,000 patient years with VNS therapy (http://finance.individual.com/display_news.asp?doc_id=PR19991215DAW043) [17].

VNS therapy: adverse events

VNS therapy is still a very new form of treatment for seizure control and as yet its long-term safety has not been established. The technique appears to be safe and well tolerated in most patients. Acutely, when the vagus nerve is actually being stimulated, most people complain of hoarseness or voice change/alteration, throat discomfort and cough [1, 5, 7, 8, 10] (http://www.efa.org/answerplace/treatment/vns.html). These side effects typically do not occur during the "off" period. Local irritation, headache, muscle pain, vomiting and nausea, dyspnea, swallowing difficulties (particularly in pediatric populations with baseline swallowing difficulties), a feeling of shortness of breath and sometimes a choking sensation have also been reported but less frequently [1, 5, 7, 14, 17, 21, 31]. Effects on the heart are minimal [6]. Tatum et al. [34] have reported intra-operative ventricular asystole during VNS in few cases.

Post-surgical infection causes problems in 2 - 3% of cases requiring removal of the device in about 1% [1, 7, 12]. Complications related to implantation procedure occur in 4% of cases and also include left vocal cord paralysis, lower facial, muscle paresis and fluid accumulation [5, 12]. Cases of migration of generator under the skin have also been reported [12].

The mechanical and technical challenges associated with VNS therapy seem to be somewhat greater and lead wires and/or generator failure are more likely to be a problem in children than in adults [7, 17]. Murphy et al. [26] conducted a study to determine the frequency of unexpected adverse events during VNS in 24 patients (4-18 years) with "pharmacoresistant" epilepsy. These patients, suffering from complex partial seizures, simple partial seizures, absence, and generalized tonic-clonic seizures, were undergoing VNS on research protocols for a total of 61 patient years. During the observation period (46 months) the investigators found 15 adverse events in 12 of the 24 patients. These included five lead fractures, two wound erythema, one abscess, and one generator malfunction after 1 year. In 11 of these 12 patients the observed adverse events required unexpected surgery under general anaesthesia.

VNS therapy has a different safety profile to AEDs. No significant cognitive, sedative, visual, coordination or autonomic side effects have been reported [1, 7, 12]. Also, it appears that VNS does not interfere with concomitant use of AEDs or other drugs [7].

Annegers et al. [2] conducted an observational study to determine the mortality and the incidence of SUDEP in 791 patients with epilepsy who received VNS

with the NCP® System, followed for 1,335 person-years. A total of 15 patients died while having VNS and 8 deaths were attributed to SUDEP. This results in a mortality rate of 6.0 per 1,000 person-years. The authors found that this mortality rate was comparable with that reported by studies of young adults with refractory epilepsy who were not treated with VNS. This analysis found that SUDEP rates were higher in those implanted with the NCP® system than those in recent drug trials but the differences were not statistically significant. The investigators speculated that the difference was due to the inclusion of more severe cases in the VNS group.

VNS therapy: advantages and disadvantages

Apparently VNS offers several potential advantages over available medical and surgical treatment [1, 7, 8, 12, 13, 27]:

- VNS has a favorable safety profile (does not cause the toxicity and impairment associated with use of AEDs) and it is associated with less severe post-operational morbidity than epilepsy surgery) and it may be preferred for some patients;
- the use of VNS is associated with incremental efficacy after VNS initiation;
- the initial cost of the device and the surgical implantation may compare favorably to the continued expenditures of chronic polytherapy with AEDs and long-term disability;
- the pre-programmed, computer-controlled characteristics of VNS permit complete and involuntary treatment compliance;
- the patient's ability to turn on the VNS therapy on-demand via the portable magnet restores an element of patient' autonomy and control over the disease; and
- VNS has no adverse interactions with other treatments.

Disadvantages associated with the use of VNS include [1, 7, 12, 13, 22, 26]:

- failure to get significant seizure reduction (the degree of seizure reduction demonstrated by VNS therapy in clinical studies is modest, and the impact of this effect on patients' QOL is not yet clear);
- the inability to predict which patients are likely to respond to it;
- the most effective stimulation paradigm has yet to be established;
- the relatively high cost of the procedure;
- it may be more difficult to perform comprehensive MRI studies after implantation of the VNS device;
- repeat surgical interventions for possible mechanical failure of the device and/or battery replacement.

UPDATE ON THE AVAILABLE EVIDENCE

The literature search revealed an increased interest in the use of VNS as a desirable alternative to new AEDs when used as an adjunctive therapy in patients with refractory epilepsy, of all ages, suffering from various types of seizures, other than partial-onset seizures. However:

- no published prospective controlled trials or other comparative studies using controls conducted to evaluate the safety and efficacy of VNS therapy for treatment of generalized epilepsy have been located;
- no published prospective controlled trials or other comparative studies using controls conducted to evaluate the safety and efficacy of VNS therapy for treatment of specific types of epilepsy in children have been located;
- no results obtained from prospective controlled studies or other comparative studies using controls have been published on the direct comparison between the use of VNS and the use of new AEDs as adjunctive therapies for seizure frequency reduction in refractory epilepsy; and
- no prospective controlled studies or other comparative studies with controls designed and conducted to determine the effect of VNS on seizure control in refractory epilepsy in terms of reduced seizure intensity/duration and AED intake in patients with refractory epilepsy or improved QOL have been located.

The best quality primary research data for this update were derived from several uncontrolled clinical studies using open treatment extension protocol that were conducted to follow-up on the safety and efficacy of VNS for refractory epilepsy in the long term. One large follow-up study included all patients who participated in an earlier controlled trial (known as E05 study). Few studies reported on subgroups of patients who participated in earlier controlled or open label trials (known in the literature as E01, E02, E03, E04, or E05 studies). The others reported results on cohorts which included patients from earlier controlled trials and added patients from open label trials. Also included were case series on the use of VNS for different types of epilepsy in pediatric populations.

The present review also included technology assessment reports published after the completion of the Technote.

The following commentary summarizes the findings from the reviewed literature.

Follow-up on VNS in patients with refractory epilepsy

The follow-up evidence, obtained from five uncontrolled studies, suggests a continuous decrease in seizure frequency with long-term use of VNS therapy. It appears that its benefits and safety do not diminish over time for those who continue to use it. However, these findings should be interpreted with caution, since the reviewed studies were also limited in other several respects. They are subject to different sources of bias, because:

- In most studies there was a large variability in patients' baseline characteristics in terms of mean age, seizure type and severity, seizure frequency, type of previous antiepileptic treatment and current medication. Many patients had more than one type of seizures.
- In all studies, reduction in seizure frequency was measured based on self-reported seizure counts.
- Studies differed in terms of patients' selection criteria, operative techniques and VNS device programming.
- Follow-up duration varied from study to study.

Ben-Menachem et al. [3] reported the outcomes of VNS for treatment of epilepsy used over a period of up to 5 years in one clinical setting. They reported the results of a prospective follow-up evaluation in 64 patients receiving VNS (average treatment time of 20 months) who were not involved in sponsored clinical trials. Patients with partial seizures (PS), Lennox-Gastaut Syndrome (LGS) or primary generalized seizures (PGS) were included. Inclusion criteria for these patients were intractable seizures despite multiple trials with AEDs, no possibility of resective surgery, or failure to improve after surgery. Forty-seven patients had PS, eight patients had LGS and nine patients had PGS. Patients were treated with 1-4 AEDs and dosages were not changed during the first 6 months of VNS therapy.

The investigators did not implant the NCP systems using "routine methodology" [3]. Range of stimulation was between 0.25mA and 2.0 mA. With unsatisfactory seizure control rapid stimulation of 7 seconds "on" and 0.2 minutes "off" was tried. The primary outcome was percentage change in seizure rates during the last 3 months of VNS compared to 3-month baseline before VNS implant. "Clinically significant reduction in seizure frequency was defined as >50% reduction of seizures (responders)". Reduction in seizure frequency was calculated as the estimates of the reduction of seizure severity was made subjectively by the patients, taking into account postictal alertness, length of seizures, injuries, and severity of the ictal state.

Overall, 29/64 patients had >50% seizure reduction (19/47patients with PS, 5/9 patients with PGS and 5/8 patients with LGS) [3]. In 11/64 patients (17.18%) the VNS device was removed due to lack of efficacy *(investigators gave no information on their characteristics)*. Among the 19 patients with PS who were responders

(and experienced a corresponding >50% reduction in seizure severity), one became seizure free and eight experienced a 75% reduction in seizure frequency. Side effects were often mild and mostly related to the time of stimulation (hoarseness in 11 patients, paresthesia in one, dyspnea in one, and throat pain in three). One patient complained about the generator placement that was moved twice without resolution. One patient developed a cord paresis after replacement of the lead. Four patients died (three in status epilepticus and one in sudden death). Based on their results, investigators concluded that "VNS is a safe and effective treatment for refractory epilepsy".

A major international open label long-term efficacy and safety study of VNS use in intractable seizures was recently published by Morris et al. [23]. They evaluated the results from 454 patients (241 male, 211 females, average age of 30.8 years, average number of years of epilepsy of 20.7 years, average number of seizures per day of 1.73) enrolled in all five clinical trials (E01 through E05) conducted from 1988 through 1997. Investigators analyzed data on 440 patients who remained available for long-term follow-up. Cyberonics, Inc. supported this work and the authors were paid consultants to Cyberonics during the course of the study.

The inclusion criteria for the five studies varied but all included patients who desired an alternative treatment for their seizures and those with persistent seizures despite appropriate medical management. The baseline frequency of seizures varied among the studies. PS were required in E01, E02, E03, E05, and generalized seizures were allowed in E04 (in 25 patients). All patients were included, even if the generator was turned off or the battery was depleted. Patients typically received VNS for 30 seconds every 5 minutes 24 hours/day but stimulation settings were adjusted to optimize seizure frequency and tolerability. All patients continued treatment with AEDs (average number of AEDs of 2.09) and new AEDs have been added during the trial. Efficacy was defined as change in seizure frequency and was reported as a percentage.

The percentage of patients experiencing at least a 50% reduction in seizure frequency post VNS implantation was 36.8 % at 1 year, 43.2 % at 2 years and 42.7 % at 3 years of follow-up [23]. The median rates of seizure reduction for all patients through years 1, 2 and 3 significantly increased at 35 %, 44.3 % and at 44.1 % from 23% at 3 months post implantation ($p<0.0001$, at each time interval). No clinically significant laboratory, Holter testing, or pulmonary function testing abnormalities were reported. Side effects most commonly reported included hoarseness in 19.8 %, headaches in 4.5%, and shortness of breath in 3.2 %. Common side effects diminished from the first to the third year of follow-up.

Change in AED intake was analyzed retrospectively only in 67 patients from studies E01 through E04. Of these patients, eight increased the number of AEDs, 18 reduced the number of their AEDs and majority remained unchanged at 2

years. The percentage of patients choosing to continue with VNS therapy at 1, 2 and 3 years respectively were 96.7%, 84.7% and 72.1% [23].

The authors concluded that VNS remains an effective, safe and well-tolerated therapy with nearly three fourths of the patients choosing to continue therapy. For many patients, it reduces seizure activity as well, or better, than it did initially with the passage of time. The authors also found that reductions in seizure frequency were not related to additional medications. Most of the medication changes occurring during the extended phase of the studies were reductions. However, the investigators commented that "adjustments of VNS settings during the trial may be responsible for improving patients outcomes".

De Giorgio et al. [9] recently reported improved VNS efficacy for refractory epilepsy in terms of seizure frequency reduction at 1 year in patients from E05 clinical trial compared with earlier trial points. The 195 patients enrolled in E05 (91males, 104 females; with ≥ 6 complex PS in 98% or generalized tonic-clonic seizures in 49%; median age at onset was 9 years; median epilepsy duration of 22 years) were prospectively evaluated over a 15-month period at 20 medical centers. Of all patients, 52% were treated concurrently with two AEDs, 29.7% were treated with three AEDs, and 18% were treated with one AED. The study consisted of an initial 3-month randomized and double-blinded phase (E05 trial) during which patients received low or high stimulation, followed by a 12-month period in which all patients received a high or active level of stimulation. The primary outcome was the percentage in reduction of total seizure frequency at 3 and 12 months after completion of E05 trial, compared to the pre-implantation baseline. An intent to treat analysis was used.

Follow-up data at 12 months after completion of E05 trial were available in 164/195 patients (84%). Twenty-two patients (14%) discontinued VNS before completing 12 months. These patients tended to be poor respondents to VNS as compared to the entire group, and the mean reduction before discontinuation for the group was 7% (range decrease of 79% to increase of 340%). At the end of the E05 trial, the median reduction in seizure frequency was 23%, and at 3 months after completion of E05 the median reduction in total seizure frequency was 34%. At 12 months the median seizure reduction increased to 45%, 35% of the 195 patients had a >50% reduction in seizure frequency and 20% of the 195 had >75% reduction in seizures.

At 3 months after completion of E05 trial the total number of AEDs remained unchanged in 91% of patients, 5% were taking more AEDs and 4% were taking fewer. At 12 months, the AEDs intake remained unchanged in 78% of patients, 1% were taking fewer AEDs and 11% were taking more. The mean number of AEDs decreased from 2.3 to 2.1 at 12 months but a change in total number of AEDs was not statistically significantly correlated with efficacy at 3 and 12 months. The percentages of patients experiencing the most common adverse events (hoarseness, paresthesis and cough) decreased over time (between 3 and

12 months). Infection was reported in 4% of patients at 3 months and in 6% at 12 months. Other adverse events which increased over time included pharingitis (in 9% of patients at 3 months and in 10% at 12 months), depression (3% to 5%) and accidental injury (9% to 15%) which was generally the result of seizures.

Based on their findings, investigators concluded that VNS is an effective long-term treatment for severe refractory epilepsy and its efficacy substantially improves over time. The investigators suggest that these data "strongly support a cumulative effect of VNS" on seizure frequency as the primary variable affecting outcome, but they discussed other factors such as dropouts, a placebo effect, removal of the active control and changes in device settings as potential causes of reported improvements. Among these they could not exclude the possibility that an increase in current intensity or a decrease in "off" time may have affected the results. Although there was no correlation between efficacy and a change in device settings, the output current and "off" time changed significantly during the 12-month period and there was a trend ($p=0.056$) toward a correlation between an increase in current and an improvement in efficacy.

Some investigators suggest that VNS therapy seems suited for use in older adults [32]. This study reviewed the use of VNS in 45 adults (≥50 years of age), at 16 sites in USA, who were treated for seizures refractory to medications. Of these, 20 patients were prospectively evaluated using data from previous RCTs (five patients from E03, 13 patients from E05) and an open label trial (two patients from E04) provided by Cyberonics, Inc. Physicians were also invited to contribute with data on 25 patients implanted after Food and Drug Administration in USA approved VNS for marketing. For the 20 patients from previous clinical trials, seizure counts and information on adverse events were collected from 3 months to 1 year after implantation. Also, adverse events from the surgical procedure were reported. Global evaluations of patient well-being as rated by an independent interviewer and the patient (using a visual analogue scale) were analyzed by comparing the last visit (approximately 16 weeks after initiation of VNS) to the first baseline visit for a significant difference. For the 25 patients from the post-approval trials the primary outcome was the percentage change in total seizure frequency during the treatment compared with the 3–month baseline. No contributor reported adjusting medications after VNS implantation.

Follow-up data were available at 3 months in all 45 patients [32]. Of these patients, 37 were 50 years but less than 60 years, seven were over 60 years but younger than 70 years and one patient was over 70 years. At 1 year follow-ups, data were available in 31/45 patients (18 from double blind trials and 13 from open label trials). Because significant demographic differences were reported between clinical trial patients when compared to open-label trial patients, all analyses were performed on the entire sample. Overall, 27% of patients had a reduction in seizure frequency by at least 50% and no patients reported worsening of the seizures at 3 months. At 1 year, 67% of the 31 patients had a

reduction in seizure frequency by at least 50%. There were no completely seizure free patients at either 3 months or 1 year. There were no reported changes in AEDs intake. Global evaluations of patient well-being were stable during baseline and after implantation then improved over time in the 20 patients for whom the data were available. The ratings by patients were higher for high VNS group than for the low VNS groups with a mean difference of 4.57 mm ($p<0.001$).

No complications related to the surgical procedure were reported. Commonly reported transient adverse events were hoarseness or voice alteration in 26 patients, coughing in 16, chest or arm pain in 12. Also reported were paresthesias in seven patients, dyspnea in four, dyspepsia in two, dizziness in two, insomnia in one, and headache in two. None of the adverse events warranted discontinuation of therapy. No drug interactions were reported in these patients who were taking two or more AEDs. There were no reported cases of bradycardia, serious cardiac arrhythmia, syncope, postural hypotension, or bladder problems.

The authors concluded by suggesting that VNS safely reduces seizure frequency and is well tolerated in older patients with refractory epilepsy (D. Ide, personal communication). They also suggested that VNS offers an advantage to older individuals with epilepsy who frequently take other medications, and also have numerous reasons for non-compliance with medications. Some important limitations to this study are related to the sample which was relatively small and not uniform. The reported results may not be generalizable to all older epilepsy populations and investigators concluded that future trials should compare VNS with antiepileptic drugs as first add-on therapy after an initial therapy fails (D. Ide, personal communication).

Vonck et al. [36] evaluated the seizure control in 15 patients (not previously included in any controlled trial) implanted with VNS with long-term follow-up (mean follow-up of 29 months, range 12-48 months). These are the first 15 of 25 patients (12 female and 13 male, mean age of 30 years, mean duration of epilepsy of 17.5 years) that have been implanted between 1995 and 1999 at one site and had sufficient follow-up data for analysis. Of the 15 patients, six had a follow-up of 1 - 2 years, five had a follow-up of 2 - 3 years; and four had a follow-up of 3 - 4 years. All patients but one were on chronic polytherapy with AEDs (mean number of AEDs being 3, range 1 - 4). replaced by “rapid stimulation” (on/off cycles of 7s/14s) in patients who did not respond to standard parameters. Data on seizure frequency, seizure type, prescribed AEDs and dosages as well as any side effects were collected. Also, reduction in seizure frequency in relation to VNS current intensity and type of cycle (standard vs. rapid), seizure type suppressed by VNS, change in duration of seizures, and duration of seizure-free intervals were prospectively assessed.

In all 15 patients there were no surgical complications and the post-operative period was uneventful. Mean reduction in frequency of complex PS from

14/month (range 2-40) to 8/month (range 0-30) was statistically significant (=0.0016). Six patients were "free of seizures" during a 12 month period and longer (four had an entirely seizure-free interval of ≥12 months, two still had simple PS but stopped having complex PS within 3 months after VNS started). Among the remaining nine patients, four had a reduction in seizure frequency of >50%, two had a worthwhile reduction between 30% and 50%, and in three patients reduction was less than 30% or seizure frequency remained unchanged. Investigators reported that a reduction in seizure frequency of 50% or higher was achieved within the first 4 months after initiation in eight patients. At the time of evaluation, 6/13 patients who frequently had secondary generalized tonic-clonic seizures (GTCS) before implantation, were free of convulsions and five of the remaining seven patients (who still experience secondary GTCS) have had a ≥ 50% reduction in seizure frequency and in duration of seizures.

The number and dosage of AEDs remained unchanged in 10/15 patients. One patient reduced polytherapy but in four patients one new AED had to be administered. In 3/4 patients free from all types of seizures, no changes of AED have been reported. The reported side effects included two mild intermittent hoarseness/voice alteration during stimulation, one dysphagia at time of stimulation, three reported persistent coughing and additional unpleasant chest throat or neck sensations during the ramping period. Patients with a ≥ 50% reduction in seizure frequency had a mean pre-implantation seizure frequency of 5.9 vs. 13.7 (p=0.0646) in the total population.

VNS in children with refractory epilepsy

Results from earlier small observational studies suggest that the therapeutic effect of VNS is better in children than in adults and that the benefit in children is achieved more rapidly. The therapeutic effect of the use of VNS as an adjunctive therapy in children with refractory seizures has been evaluated in several follow-up uncontrolled studies with open-label add-on designs and small sample sizes. Overall, results of earlier studies [15, 20, 24] and from more recently published series [25, 28] suggest that VNS reduces seizure rates in children by 20 to 30% within 3 months, and by 40% to 50% after 18 months to 24 months of therapy. However, these results must be interpreted carefully because of the uncontrolled, open-label designs, inclusion of children in different age groups and with a variety of epilepsy syndromes, different stimulation paradigms used, differing periods of follow-up, and the varied and changeable AEDs co-administered.

Murphy and the Pediatric VNS Study Group reviewed the experience with VNS in prospectively studied pediatric populations with "pharmacoresistant" epilepsy [25]. Sixty children who were entered into controlled or compassionate protocols of VNS had been monitored for at least 3 months after the devices were activated. A stimulation "on"/"off" cycle of 30 s/5 min. was used. Sixteen of these patients were younger than 12 years (age range: 3.5 to 18 years). Of all patients, 56.7% suffered from complex PS, 26.7% had GTCS, 6.6% had simple PS

and 10% had PS and secondary generalization. Investigators give little information on the clinical profile of these children (of whom the majority were adolescents) [5]. In two thirds of all patients the etiology of epilepsy was unknown and it is not known whether the children were intellectually or neurologically normal, features often associated with intractable epilepsy in children.

After 3 months of VNS therapy, a median reduction of seizure frequency of 23% occurred in all 60 patients [25]. At 6 months, the median reduction was 31% in 55 patients, at 12 months it was 34% in 51 patients, and at 18 months it was 42% in 46 patients (over 18 months after implantation, there was a reduction in seizure frequency of about 50%). Improvement was not associated with any seizure type or cause. Three patients who did not respond dropped from the study. In 16/60 patients younger than 12 years of age, the results appear similar to those of the group as whole. These patients were all in the compassionate use protocol and generally had more severe seizures than the older children in the controlled protocols. The authors concluded that age appeared not to be a factor in the efficacy of VNS.

Adverse events occurred in 10% of patients and included fever, cough, headaches, voice alteration, and congestion/cold. None of these necessitated cessation of VNS and their frequency decreased in time (as reported at every 3 months). Holter monitoring revealed no abnormalities. Complications (defined as serious events caused by treatment) included one aspiration pneumonia (*the patient died*) and one necrosis of the skin overlying the generator (*the device eroded through the skin; no further information is available on this patient*). Some of the patients (*the authors do not specify how many*, *their age and/or other characteristics*) required surgery under general anesthesia, to repair a fractured lead or to replace a defective generator and the surgeries. In general, the device was well tolerated. Five children discontinued VNS use.

The investigators concluded that VNS appears to be a safe and effective adjunctive therapy for the treatment of children with epilepsy intractable to available AEDs. The observed reduction in seizure frequency improves over time (relative to baseline) with a greater reduction at 18 months than at 3 months. The investigators mentioned that specific disorders such as absence epilepsy and conditions such as pregnancy were not studied. They recommend the use of VNS only for pediatric patients who have had many other AED therapies that have failed and concluded that a controlled trial in children will be necessary to definitively prove efficacy.

During post VNS implantation follow-up visits output current was gradually increased until tolerance or a maximum of 3mA was reached (mean 2.25 mA). ”Standard stimulation” (30 Hz, 0.5 ms, of/off cycles of 30s/300-600s) was time (relative to baseline) with a greater reduction at 18 months than at 3 months. The investigators mentioned that specific disorders such as absence epilepsy and

conditions such as pregnancy were not studied. They recommend the use of VNS only for pediatric patients who have had many other AED therapies that have failed and concluded that a controlled trial in children will be necessary to definitively prove efficacy.

Parker et al. [28] prospectively studied the effect of VNS in 16 children with epileptic encephalopathy attending one site. Epileptic encephalography was defined as the occurrence of mixed generalized seizures with a diffusely slow EEG with generalized or multifocal interictal paroxysmal abnormalities. Clinical and EEG findings were used to classify children into different syndromes according to the International League Against Epilepsy (ILAE) and leading authorities. Seven children were classified with infantile spasms developing into LGS, three with novo LGS, four with severe myoclonic epilepsy of infancy, and two with myoclonic astatic epilepsy (mean age at seizure onset of 16 months and at implant 11 years). Seven or more AEDs were used before implant in 12 children and three to six in the other children. Caregivers were requested not to change AEDs during trial. Seizure frequency was recorded for at least 8-week baseline period before and for 1 year after implant by the children's parents using their own description of seizures in a diary. The principal investigator reclassified these according to recommendations in the ILAE.

The stimulation started at 0.25 mA for 30 seconds every 360 seconds and was increased to a maximum of 1.5-2.0 mA depending on tolerance. Children were subsequently reviewed every 4 to 8 weeks. After 6 months, six children with a <50% reduction in seizure frequency were offered stimulation at 0.75 to 1.25 mA for 7 seconds every 19 seconds. After 4-8 weeks the seizure frequency on the rapid cycling was compared with that between 6 and 12 months after implant. Seizure severity was assessed in the quality of life (QOL) questionnaires.

One year after implant, four had >50% reduction and two had a >50% increase in seizure frequency. The median reduction in seizure frequency compared to baseline was 17% in 15/16 patients (p=0.264). One device was removed because of infection. All 9 children with LGS and those with LGS preceded by infantile spasms had a median reduction of 34% (p=0.14 and p=0.13, respectively). Two children with novo LGS had a 100% decrease and a 40% increase, respectively. Four children with severe myoclonic epilepsy of infancy (SMEI) had a median increase of 31% (p=0.29) and two children with myoclonic astatic epilepsy had a 0% and 67% reduction, respectively. More rapid cycling (7s "on"/19s "off") compared with conventional stimulation (30s "on"/ 5 min. "off") did not lead to a reduction in seizure frequency in any child. There was no trend toward improvement of the EEG. The investigators concluded that VNS did not statistically significantly improve seizure frequency, severity, adaptive behavior, or the EEG during the first year of treatment, for the group as a whole, although four children (27%) had a worthwhile reduction in seizure frequency.

It has been emphasized that an important objective of treatment in patients with refractory epilepsy must be significant improvements in QOL [6, 10, 37]. Effects of VNS on the QOL of children and their caregivers have been addressed in earlier studies [15, 20, 24] which used written visual analogue scales completed by caregivers to assess the children's overall QOL at various intervals. The follow-up periods in these studies ranged from 2-30 months. Investigators in these studies reported improved QOL scores and some results indicated that QOL scores corresponded with the reduction in seizure frequency in most patients. Specific reported improvements included improved learning and social skills, reduced postictal lethargy, newly toilet trained, increased general activity level, and newly acquired self-feeding and speech.

Parker et al. [28] performed an extensive quantitative battery of QOL, cognitive, and behavior assessments on their 16 children treated with VNS after 1 year. The children's parents were asked to complete a questionnaire on which areas of their children's lives they would like to see change in addition to any possible reduction in seizure frequency. Using this information further assessments were conducted using the Vineland Adaptive Behavior Scale and the Wellcome QOL Assessment (developed for children with LGS) which were performed on all children before and 1 year after implant. In children with less severe learning difficulties, the British Picture Vocabulary Scale (BPVS), Leiter International Performance Scale and Conner's Parent/Teacher Rating Scales were administered before, and 1 year after implant.

There was no trend toward improvement of the adaptive behavior. There were no significant differences between age equivalents pre- and post-implant in either the communication, living or socialization domains for the Vineland Adaptive Behavior Scale ($p=0.26$, $p=0.33$, $p=0.78$, respectively). An analysis of QOL showed a "significant improvement in perceived treatment side effects and general behavior" ($p=0.02$ and $p=0.01$, respectively). These improvements did not correlate with changes in seizure frequency ($p=0.22$ and $p=0.78$, respectively) and there was no significant change in the other domains ($p=0.837$- 0.225). The investigators reported no significant changes in communication, daily living skills, socialization, seizure severity, seizure-related injuries or mood (Vineland, Wellcome scales) or hyperactivity (Corner's Parent and Teacher Rating Scale). In their answers to a single question on change, most parents felt that "overall their child had improved compared with baseline". In six children undergoing further assessment, there was a statistically significant improvement in verbal performance, which did not correlate with reduction in seizure frequency. Overall the results reported by these studies suggest that VNS improves QOL in children, but there was no clear message in relation to the correlation between QOL and observed changes in seizure frequency. These results also need to be interpreted cautiously because all studies were uncontrolled and used open label add-on designs. The results are susceptible to placebo effects and to reporting

bias on the part of the children and their caregivers. The tools used to assess QOL and the follow-up periods varied in these studies.

VNS for patients with LGS

Many publications on the use of VNS for refractory epilepsy have included children with LGS in their study population but only six have reported findings from these patients separately [3, 15, 16, 18, 20, 28]. Labar [17] pooled together and discussed the results of VNS for 28 children with LGS described in five separate studies [3, 15, 18, 20, 28]. All studies used open-label add-on trial designs and, in general, their authors compared seizure rates of VNS treatment at 2-month baselines (range 1-6 months) with rates after 18 months (range 6 -29 months). Mean age at VNS implantation was 14 years (range 4-44 years). AEDs were not changed in two studies and changed after 6 months of VNS in two other studies. In the fifth study, changes in AEDs were accepted in combination with VNS therapy (during 21-29 months of follow-up, the mean number of AEDs was reduced from 2.6 to 2.3). The five studies combined had a mean seizure rate reduction of 55% (34%-90%). Ben-Menachem et al. [3] noted that GTC and absence seizures responded better to VNS than other seizure types. Three of the five reports specifically stated that no particular seizure type responded better than any other [18, 20, 28]. This issue was not addressed in the remaining paper [32].

Labar compared these results with those of treatment with some investigational AEDs (felbamate, lamotrigine, and topirimate) when used in other trials as adjunctive therapy to treat the refractory seizures of LGS [17]. He concluded that VNS may prove to be safer, more tolerated and more effective than these AEDs when used as adjunctive therapies for LGS. However, these results were not directly comparable because of different approaches used. The lengths for baseline phase and for treatment phase were different. Also different were the designs and protocols used for these studies. Even the patients' characteristics seemed to be different. Also patients on felbamate received stable maintenance doses during treatment phase while VNS parameters changed and some AEDs or their dosages changed during treatment phase with VNS.

Labar also compared data obtained from a study conducted to determine efficacy of corpus callosum section (CCS), an epilepsy surgery used in patients with LGS [17]. He concluded that CCS has a greater effect on epilepsy that VNS in patients with LGS but it involves more risks and it is irreversible. For the comparison, Labar cited results of CCS in patients with LGS but does not give any details about the study the data were obtained from. It was not clear how comparable were the patients treated with CCS and those treated with VNS. These comparisons and the conclusions drawn from them should be considered cautiously since the cohort of patients with LGS treated with VNS represents the total of patients treated in five studies (open-label add on designs, who are different in many aspects).

Recently Hosain et al. [16] reported on a single-site experience with VNS for LGS in 13 patients (ten males and three females; median age of 13 years, range 4-44 years; eight patients were under 18 years of age, range of 4-15 years; five patients were adults diagnosed with LGS). All patients had LGS, with severe medication-resistant mixed seizures, static encephalopathy and generalized slow spike-and-wave discharges seen on EEG. Using historical clinical data, and ictal and icterictal EEG findings, seizures were classified as tonic, atonic, atypical absence, myoclonic, GTC or complex partial. Three patients had previous CCS and six patients previously failed ketogenic diet.

After 1-month of baseline seizure counts, VNS was implanted and activated after 2 weeks from implantation in 5/13 patients and on the first postoperative day in the remaining eight patients. Stimulation intensity was adjusted to the maximum tolerated, with other parameters held constant for first 3 months (average current intensity was 0.75 mA, range of 0.5 – 1.75 mA). Standard cycling was used in all patients (30 sec "on"/5 min "off"). Caregivers used on-demand stimulator activation with the hand-held magnet. In the first five patients no changes were made in AEDs intake and in the remaining eight adverse events changes in AEDs were allowed only after the first 2 months of VNS therapy. The primary efficacy measure was the comparison of seizure rates during a 1-month baseline with median seizure rates over the entire 6 months of VNS. AEDs blood levels at baseline and after VNS were also compared.

During the first 6 months of therapy, VNS produced a median seizure rate reduction of 52% (range 0% to 93%; p=0.4). Five patients had <50% reduction in seizure frequency, one patient had no change in seizure frequency, two had >50% reduction, and five had >75% reduction. The investigators reported no seizure-free cases. None of the patients discontinued VNS therapy. Among the eight patients who were under 18 years of age, one had no change in seizure frequency, three had <50% reduction, one had >50% and three had >75%. There was no difference between blood AEDs levels at baseline compared to levels after 6 months of treatment with VNS (p=0.6). Overall, six patients were able to reduce the total number of AEDs administered by at least one agent after 2 months of VNS. Most common side effects included hoarseness, coughing and pain in the throat when VNS was on but their frequency decreased over time. One patient experienced incisional infection. No cognitive behavioral motor or coordination side effects were reported.

Based on their results, investigators suggested that VNS is well tolerated and is an effective adjunct therapy for patients with LGS in terms of reduction in seizure rate. These results need to be interpreted cautiously since they were obtained in an open label add-on design with a short follow-up and a small sample size that included children, adolescents and adults and relied on self-reported counts (susceptible to reporting bias on the part of the patients and their caregivers). Investigators concluded that large, multicenter collaborative

blinded studies are needed to prove the efficacy of VNS and other therapies for LGS.

VNS in generalized epilepsy

Most of the clinical trials on the use of VNS therapy focused on patients with refractory partial seizures. The efficacy of VNS therapy for generalized seizures has not yet been demonstrated.

Labar et al. [18] described the use of VNS therapy in 24 patients (13 males and 11 females) with generalized epilepsy (only generalized seizures and only generalized epileptiform activity in 23 patients or generalized slowing on EEG in one patient). These patients were part of a larger group studied in an earlier multicenter, prospective open label trial (EO4, supported by a clinical research grant from Cyberonics). To be included, patients were required to have one or more seizures per month, be older than 3 years, and have no cardiac or progressive neurologic disease.

Seven patients had idiopathic epilepsy and 17 patients had symptomatic epilepsy. Eleven patients had multiple seizure types. Median age at implant was 18 years (4-40 years) and median age at epilepsy onset was 2 years (0-14 years). Median duration of epilepsy was 15 years (4-35 years). Reported median number of AEDs at implant was two (1-5) and median number of seizures in baseline months was 48 (2-1650). After 1-month baseline, the VNS system was implanted and stimulation parameters replicated the "high stimulation" values used for patients involved in the earlier RCTs. Patients did not change AEDs during study.

Primary outcome was percent change in seizure rate in the first 3 months of VNS compared with a 1-month baseline. For all types of seizures in all patients, VNS produced a median seizure rate change of –46% (range –85% to +130%) (p=0.004). Sixteen of the 24 patients had "better than a –30% reduction" and 11/24 patients had "better than a –50% reduction in seizure rate". GTCSs had a median change of –41% (range –100% to +350%) (p=0.029). One 12-year-old patient with symptomatic epilepsy and one 10-year-old patient with idiopathic epilepsy had increased seizures (+130% and +60%). Among patients with symptomatic epilepsy, VNS produced a median seizure rate change of –40% (range –85% to +130%) (p=0.037) and for those with idiopathic epilepsy the median seizure rate change was –60% (range –84% to +60%) (p=0.332). All adverse events were "mild" except "moderate" cough and one "moderate" anorexia. One patient had an incisional infection. The median heart rate at 3 months was lower than that at baseline. Holter monitoring before and during VNS did not show arrhythmias or bradycardias.

Based on their results and analyses, investigators suggested that "VNS is an effective treatment for medication-resistant generalized epilepsy even in patients

as young as 4 years". Patients with higher seizure rate at baseline and older age at epilepsy onset had the best responses to VNS.

Findings from other health technology assessments

In December of 1998 ECRI published a report on the current state of knowledge of VNS for treatment of intractable epilepsy in children and adults. Investigators included in this review all published studies (1974 to June 1998) on the effect of VNS on seizure frequency. They excluded studies published in abstract form and studies describing only subgroups of the patients from one or more studies. Also excluded were preliminary reports of study results if a complete report of that study was available.

Based on their findings, ECRI investigators concluded "VNS appears to be a reasonably safe and effective adjunctive therapy for some patients with epilepsy who cannot be controlled by standard pharmacotherapy or surgery [12]. They also concluded that:

- neither tolerance nor progressive adverse effects have thus far been demonstrated, and the effects of VNS for periods greater than 2-3 years are still unknown;
- the average effect of VNS therapy on seizure frequency is modest, with reported reductions of approximately 30%;
- methods for determining whether or how well a patient will respond to VNS have yet to be established;
- the effect of VNS on patients with low seizure frequency has not been established in clinical trials;
- whether this reduction in seizure frequency represents a significant improvement in these patients' lives remains to be determined; a large reduction in seizure frequency may still leave a patient with an intolerable number of seizures, resulting in social difficulties and inability to perform basic tasks.

In 1999, the American Academy of Neurology Therapeutics and Technology Assessment Subcommittee published the results of an update on the use of VNS for epilepsy [13]. The update focused on the information obtained from clinical studies on the use of VNS in both children and adults that were published after their first assessment in 1997. The committee concluded that there is sufficient evidence "to rank VNS for epilepsy as effective and safe based on preponderance of Class I evidence". VNS is indicated for patients over 12 years of age with intractable partial seizures "who are not candidates for potentially curative surgical resections". The degree of improvement in seizure control from VNS remains comparable to that of new AEDs but is lower than that of mesial temporal lobectomy in suitable surgical resection candidates. In the opinion of this committee:

- insufficient data are available to permit definitive statements regarding the relative risks and benefits of VNS in children younger than 13 years of age;
- patients should undergo a thorough evaluation of their condition to rule out non-epileptic conditions or treatable symptomatic epilepsy before they are considered for VNS therapy;
- when magnetic resonance imaging (MRI) is indicated, it is preferably to be obtained before VNS implantation, because data are insufficient to allow conclusions of MRI safety after implantation;
- insufficient data are available to identify which patients are likely to benefit from VNS;
- the population studied in pivotal trials on VNS were refractory to standard therapy and may represent a particular challenge to new therapies;
- because VNS therapy rarely causes complete freedom of seizures, and it is moderately invasive and expensive, its use is more appropriate in individuals unable to tolerate or benefit from AEDs and for whom a partial reduction in seizure frequency will significantly improve their QOL;
- efficacy of VNS in less severely affected patients remains to be evaluated;
- some patients appear willing to undergo implantation of VNS to avoid usual undesirable effects of antiepileptic medication.

EVIDENCE OF EFFICACY OF VNS

The goal of surgery for epilepsy is to improve functioning and well being through reduction in seizure frequency, seizure severity and AED intake [35]. The primary outcome used to measure efficacy of VNS in all reviewed studies was a change in seizure frequency (relying on self-reported seizure counts by patients or caregivers), usually expressed as the percent change in seizure frequency after the initiation of VNS therapy as compared to baseline. The number of patients achieving at least a 50% reduction in seizure frequency was another commonly reported outcome.

These outcomes are subject to variability due to the difficulty patients and/or caregivers have in detecting and reporting seizures [12]. Also, by using these outcomes as measures of VNS efficacy may result in missing important effects. These outcome measures do not include objective assessment of the beneficial or deleterious effects of treatment on changes in seizure severity, development, behavior or QOL, any or all which may be considered more important by the patients and their caregivers [10, 28]. Some patients experience many seizures per day and a 50% reduction may not translate into great improvement in their QOL

since residual seizures may continue to preclude them from living a normal life [1, 10, 12, 16].

The reviewed studies included patients with different demographic and clinical characteristics and their response to VNS was variable (some patients had major and/or rapid response, other had little or no response). For this reason, the mean or median seizure reduction reported in the published studies cannot reflect each patient's experience [12].

Earlier studies suggested that reduction in seizure duration and intensity may be achieved following VNS but no numerical data were supplied [12]. Although some of the reviewed follow-up studies reported on these effects, these results have not clearly demonstrated that VNS itself alters seizure duration or intensity in patients with refractory epilepsy.

Some studies reported on patients' ability to abort seizures by activating the VNS magnet but only limited data have been reported on the success rate. Since the patient's ability to abort seizures is likely to have a positive impact on patient's compliance and QOL further research is warranted to quantify this impact [12, 22, 27, 32].

AED therapy is continued after implantation in all patients treated with VNS. In most studies patients did not alter their AED intake during the study period. Patients experiencing a reduction in seizure frequency usually do not reduce their usage of medication therapy in terms of number of AEDs or dosage of the same AEDs. To date, no AED intake-reduction studies have been reported and it is still not established whether the use of VNS as an adjunctive therapy in patients with refractory epilepsy will enable them to decrease their drug intake.

The reviewed literature suggests an increasing interest among investigators in using patients' QOL as an important outcome measure in the treatment of epilepsy. There is evidence to suggest that QOL is markedly improved only if the patient was completely free of seizures after epilepsy surgery [35] and some investigators believe that this conclusion should be true for efficacy of other epilepsy treatments [16]. With VNS, it is not yet clear whether the reported reductions in seizure frequency are sufficient to have a positive impact on the patient's QOL [12]. Also, if complete freedom from seizures is the goal of the therapy, this is not likely to be achieved with VNS since only a few patients achieved that result in the reviewed follow-up studies. According to Cyberonics, Inc. one-third of patients treated with VNS experienced a profound improvement in overall QOL, one-third experienced a good improvement in overall QOL and one-third experienced little or no improvement [8]. Although in most reviewed studies global evaluation scores indicated overall satisfaction with the treatment, scores did not correlated with changes in seizure frequency in all cases. There is a need to document the effect on QOL achieved by reducing intractable seizures by 50%, 75% or even 90%.

Patient satisfaction with VNS has been measured by patient continuation rates that were "97% at one year, 85% at two years and 72% at three years" in one follow-up study [9].

Some of these observations may indicate areas for future investigators to examine the value of VNS therapy in the management of refractory epilepsy in both children and adults more closely.

DISCUSSION

It appears that currently VNS has a place as a last-resort approach to these patients. Some investigators suggest that it may even be considered as a more desirable alternative to new AEDs including experimental drug trials [1, 13]. However, VNS is a palliative, not a curative, therapy and should not be considered as an alternative to conventional methods of AED therapy and epilepsy surgery. Patients should undergo extensive and thorough epilepsy evaluation and testing before VNS is considered so that a definitive diagnosis of epilepsy syndrome can be made and other treatment options such as medications or epilepsy surgery have been ruled out.

The definition of refractory epilepsy differs from centre to centre *(when the definitions are available)*. Standards from previous controlled trials commonly required for a seizure frequency of at least six seizures/month and a seizure-free interval of no longer than 2-3 weeks despite therapy with multiple AEDs [1, 6, 7, 12]. However, seizure frequency, seizure type, severity of attacks, drug toxicity, and overall impact on QOL must all be considered before a patient is deemed refractory to AED therapy [1, 16, 29]. Adequate monitoring of patient compliance and sufficient trials of AEDs must also be assured [1, 10, 13, 16, 30].

The VNS therapy has proven beneficial effects for seizure control in terms of reduction in seizure frequency in patients (≥12 years of age) with partial onset seizures that are refractory to medication and the reviewed literature indicated that there is incremental improvement over time. A trend towards improved seizure control with longer use of VNS was observed and appears that response during the first 3 months of therapy is predictive of long-term response. However, there are still unanswered questions and issues associated with the use of VNS in patients with refractory epilepsy:

- There are no clear predictors for non-responders in the reviewed clinical studies. Predictors of outcome based on pre-implantation data remain elusive. Patients and families need to be counseled prior to implantation so that expectations are realistic.
- The effect of VNS in less severely afflicted patients also remains to be determined.
- The average reduction in seizure frequency as reported in most studies is modest and few patients achieved complete freedom of seizures after VNS.

- Data are still needed to determine the impact of VNS on patients' QOL.
- How different stimulation paradigms influence clinical response to VNS is not clear yet.
- Most investigators identified a clear need for additional research on the use of VNS in children with refractory epilepsy before its adoption for clinical use.
- The efficacy and safety of VNS use for generalized epilepsy has yet to be established.
- At present, it appears that VNS is safe and well tolerated. However, VNS is a relatively new therapy and the possibility of as-yet-undiscovered adverse events in the long-term associated with its use still exists.
- The mechanism of action for VNS therapy is still unknown**.**

The main issue in further establishing the clinical efficacy of VNS in the long term is to identify the best responders. However, it has not been determined yet whether there are specific types of epileptic seizures or epileptic syndromes, which respond better to VNS, and it remains unknown how to best select patients who may benefit from VNS. Some investigators suggested the use of VNS therapy as a surgical option for patients (≥12 years) with medically refractory epilepsy who are not the ideal candidates for "potentially curative surgical resections" [13]. Others include VNS among the common epilepsy surgical procedures, as one procedure to be used for all types of seizures, and all EEG abnormalities [5].

CONCLUSIONS

The reviewed literature suggests that VNS therapy is safe, well tolerated and effective when used as adjunctive therapy in patients (>12 years of age) with partial-onset seizures refractory to medication, who are not candidates for epilepsy surgery or failed surgery. Since the previous review [7], limited follow-up evidence reported by uncontrolled studies suggest a continuous decrease in seizure frequency with long-term use of VNS therapy. It appears that its benefits and safety do not diminish over time for those who continue to use it.

However, questions remain on the mode of action of VNS, which patients are likely to respond, the effect of VNS in less severely afflicted patients, the effect of VNS in different syndromes of epilepsy, and QOL of treated patients and their caregivers. Further research is needed on these aspects and on the details of stimulation paradigms such as different stimulation protocols (rapid cycle, early activation, duration of on/off cycles) and use of VNS in different syndromes of epilepsy.

Patients considering VNS therapy and their caregivers should be aware that:

- VNS therapy appears to have a moderate initial efficacy that may increase over time but it is not a cure for epilepsy.
- VNS should only be used as a last resort after an extensive and thorough patient evaluation to rule out non-epileptic conditions and exclude patients who may benefit from available AED therapy and epilepsy surgery.
- VNS does not work for everyone.
- The safety and efficacy of VNS in children with refractory epilepsy has yet to be established.
- VNS appears to have a favorable safety profile when compared to conventional therapies but the possibility of unknown adverse effects associated with its use still exists.

SECTION 2

VNS THERAPY IN CANADA: SURVEYS SUMMARY REPORT

This section is divided into two parts: a summary report on a survey of the medical directors across Canada, and a summary report on a survey of the manufacturers of the device used in vagus nerve stimulation.

The use and coverage of VNS therapy in Canada: survey of Provincial and Territorial Medical Directors of Health

This survey was conducted as part of a request from Alberta Health and Wellness to explore the coverage and reimbursement for surgical services and devices associated with vagus nerve stimulation across Canada. The survey was either (1) completed by fax and clarified by telephone if necessary, or (2) conducted by telephone follow up only (see Appendix A, section on "Methodology for surveys").

Of the twelve total respondents, method (1) was employed with seven of the respondents, and method (2) with the remaining five. Table 1 provides a quick summary of the response patterns across the country for each topic. Detailed discussion follows. Detailed discussion follows.

Table 1: Response to VNS Survey Questions

Province/Territory	VNS Offered There	Surgical Procedure covered	VNS Device covered	Limitations by diagnosis of epilepsy	Limitations by age
British Columbia	Yes	Yes	Yes	Yes	No
Yukon*	No	Yes*	Yes*	Yes*	No
Alberta	Yes	Yes	Yes	No	No
North West Territories/ Nunavut	No	No	N/A	N/A	N/A
Saskatchewan	No	Yes	Yes	Yes	No
Manitoba	Yes	Yes	Yes	No	No
Ontario	Yes	Yes	Yes	No	No
Quebec	Yes	Yes	Yes	No	Yes
Nova Scotia	Yes	Yes	Yes	No	No
New Brunswick**	No	Yes**	Yes**	No**	No**
Prince Edward Island	No	Yes	Yes	No	No
Newfoundland	Yes	Yes	Yes	No	Yes
Total 'Yes' responses	**7/12**	**11/12**	**11/12**	**3/11**	**2/11**

* They accept the policies of the province they are referring to, which is usually B.C.

** They accept the policies of the province they are referring to, which is usually Nova Scotia

Eleven of the twelve responding Ministries of Health do cover this procedure and the device through their medical insurance programs, and hospital budgets. This has changed since the project undertaken by AHFMR in 1998 [7]. At that time provinces and territories were not covering the cost of this procedure or the device. VNS is not available or covered in the Northwest Territories/Nunavut. The procedure is available in seven provinces, while three provinces and one territory provide coverage for the procedure to be done in another province. These out-of-province costs are usually covered through the reciprocal agreements.

Of the eleven provinces/territories covering this procedure, nine indicated that the overall appropriateness of this treatment for an individual patient was determined by the clinicians, not the Ministry. In the other two, BC and Yukon, it is not stated outright, but the applications for the procedures to be done, come from the clinicians requesting the Ministry for approval of coverage; therefore, the clinician still plays a key role in determining the appropriateness of this treatment for a patient.

Questions regarding replacement and lifetime limits of coverage for the procedure or the device did not produce results that provided additional information, as the questions were somewhat difficult for the respondents to answer. Many of those surveyed, pointed out that of course they would continue to cover the costs of replacing a device that they had approved to be implanted in the first place, if it continues to be effective. The clinicians and specialists, not the Ministries, would determine this effectiveness. Three respondents likened vagus nerve stimulators to cardiac pacemakers when it came to coverage and replacement. Questions on limits were also difficult for most of the respondents to answer, as the issue has not arisen yet, with such a newly funded technology. There were no differences in coverage for children and adults.

Regarding coverage limitation by diagnosis of epilepsy, the number of yes and no responses need further explanation. Three individuals did state a diagnostic limitation within 'epilepsy'; Saskatchewan indicated a diagnosis of **complex** refractory epilepsy, British Columbia indicated it for recurrent/refractory **partial onset** seizures, and Yukon would follow the policy of BC. Though not indicating a specific diagnosis of epilepsy, another four, Alberta, Newfoundland, Nova Scotia, and Quebec indicated it for those with intractable or refractory epilepsy, or those who had not responded to the 'around five traditional medications', 'normal medication treatments', or 'other treatments', respectively.

Of the eleven provinces/territories that cover VNS, only two had any age limits set, and these were more determined by the judgements of their specialists. In Newfoundland, there is a minimum age of three, which is based largely on the size of the child in relation to the insertion of the device. Quebec has an age limit of two years, but again uses the judgement of their clinicians to make that

decision. In addition to these two provinces basing the decision on the set age for treatment on a clinicians' recommendations, three other provinces, Nova Scotia, PEI, and New Brunswick, stated decisions regarding the appropriateness of the patient's age for treatment were determined by the clinician.

Additional comments were made, with a few key issues being iterated across the respondents. Saskatchewan, Quebec and British Columbia all discussed issues about the lack of proven effectiveness of the treatment and the need to improve the diagnostic indicators or the selection process for those individuals who will most likely respond. It is an expensive treatment, and has had a low success rate overall. These issues were all identified in the project undertaken in 1998 [7] as being questions that needed to be explored and answered. Quebec found that VNS seemed to be more successful with their pediatric patients than their adult patients, which was also a general finding in the AHFMR Technote [7]. Quebec is currently conducting a survey across their province of all neurotransmitter devices to explore what are currently being used and what is needed. Alberta and others are also having discussions around whether the device itself will/should be covered by the province or the individual regions within a province.

Available VNS devices (models, components, prices): survey of manufacturers

A second survey was conducted to explore the manufacturers of the VNS devices, the different components within each device and the costs of each component.

The search of the manufacturers of this device found that there is currently only one manufacturer in the world for the VNS devices available on the market. All the devices named in the literature and on the identified web sites were the same – the NeuroCybernetic Prosthesis (NCP®) System manufactured by Cyberonics, Inc., Webster, Texas, USA. Therefore the survey is of this manufacturer and was conducted with the Xycorp Medical Inc., which is the Canadian distributor for Cyberonics, Inc.

A representative of the Canadian distributor was contacted to provide information on the device. The questions asked were in relation to three main categories: prices of the device and its components; differing costs for children and adults; and replacement costs for each component of the system. Table 2 contains a summary of the information on the components that need to be purchased for each patient (D. Ide, personal communication). Each NCP System purchased includes one generator, one lead, and one tunneling tool. Both magnets come with the purchase of the system. Prices are in Canadian dollars unless otherwise stated.

Table 2: Summary of VNS Devices from Cyberonics, Inc.

Device	Model	Price	Replacement
Generator	100	$ 9,980.00	Approximately 4-5 years (battery life)
Generator	101	$ 12,200.00	Approximately 12 years (battery life)
Lead	300-20	$ 2,695.00	None
Lead	300-30	$ 2,695.00	None
Tunneling tool	400	$ 295.00	N/A
Magnets (block & horseshoe)	220-1 and 220-2	$30.00 USD each	Only if misplaced

The Model 100 Generator was the first one on the market, and has been around for approximately ten years. The Model 101 Generator is smaller than the 100 and has a much longer battery life. It will likely end up replacing the 100, which will be phased out. When the battery life has been reached, the entire generator needs to be replaced. The approximate battery life recommended by the manufacturer is shown in Table 2, but will vary according to the device settings being used with a particular patient. The bipolar lead has two electrodes that go around the nerve, and comes in two sizes to allow for the best fit with the individual nerve. The 300-20 lead has a 2mm helix and is the most commonly used. The 300-30 has a 3mm helix, and is seldom used. Either lead, however, can be used with either generator; they are completely interchangeable.

The Model 400 tunneling tool is a disposal tool used during the implantation procedure. The 220-1 is a block shaped magnet, and the 220-2 is a horseshoe shaped magnet. One of each is provided with the NCP system. Sizes and costs for any of the components are the same for both children and adults. The computer, programming wand and programming software are items that are provided free of charge to the specialist who is performing the procedure, and are used for multiple patients.

The Canadian distributor has also been contacted to provide an estimate of how many VNS devices have been and will be distributed in Canada for routine care of patients with refractory epilepsy. According to the representative of Xycorp Medical Inc. there have been approximately 150 units implanted in Canada to date (as of October 2000) and it is expected that another 100 units will be implanted over the next 10 month. It is not clear from these estimates how many units have been used and will be used only for routine care of patients with refractory epilepsy and how many were used and will be used in research studies on the effect of VNS for other indications (J. Ide, personal communication).

The representative of the Canadian distributor for VNS devices mentioned that other applications of this technology are approved and to be approved in the future for additional indications such as depression, tremors, and obesity (J. Ide, personal communication). The same device and lead will be used.

APPENDIX A: METHODOLOGY

Methodology for literature review:

An electronic search (1998-September 2000) was conducted for articles/papers pertaining to the subject, which reported on human subjects (in all age groups) and were published in English. The databases searched included MEDLINE, EMBASE, HealthSTAR, PubMed, Cochrane Database of Systematic Reviews, ECRI Database, Best Evidence Database, and NHS (UK) Centre for Reviews and Dissemination Databases. In addition, a search of the relevant web sites was conducted. The following is a summary of the literature search strategy used:

- Words used in the searches included textword and subject headings of: vagus, vagus nerve, vagus nerve stimulation/stimulator, vagal nerve stimulation/stimulator, nerve stimulation/stimulator, electric stimulation/therapy, nerve stimulation, electro/electric nerve stimulation, epilepsy pacemaker, epilepsy, seizures, cost, safety, efficacy, effectiveness. These were searched independently and in combination.
- *Medline* was limited by: clinical trials (all subheadings), research design, follow up studies, program evaluation, quasi-experimental, case control study, epidemiologic studies, or retrospective studies.
- *Embase* was limited by: clinical trial (all subheadings), clinical study, case control or control study. It was also limited by: cost or cost effectiveness (all subheadings); safety or danger, risk, safety and related phenomena; and efficacy, relative biologic effectiveness, or effectiveness.
- Pubmed was searched for 1998-2000 and Premedline, was narrowed by articles already retrieved through other searches.
- All other databases were searched for vagus, vagus/vagal nerve, vagus/vagal nerve stimulation, electric stimulation/therapy.
- The Internet was searched using "vagus nerve stimulation", and "vagus nerve".

For each citation considered, the abstract was read (when available), and articles were excluded if they were outside the scope of the review. A selection was made and full articles that were published after November 1998 and met the following criteria were retrieved:

- articles reporting results of clinical studies conducted to examine safety and efficacy of VNS, effectiveness of VNS as a treatment for patients with refractory epilepsy;
- articles reporting results of studies conducted to determine quality of life (QOL) in people with refractory epilepsy who had VNS device implanted;

- reviews, technology assessments, commentaries, discussions, position papers, consensus statements, background documents and brief communications on advantages and disadvantages of VNS, cost implications, efficacy/effectiveness of VNC, cost-effectiveness, clinical utility of VNS, clinical utilization, QOL after use of VNS for this indication;
- editorials, only if they provided pertinent information on the issues discussed.

Studies published only in abstract form, letters, case-reports, studies on animals and technical reports were excluded. Also excluded were any articles reporting on the use of VNS for other indications.

The bibliography of each of the retrieved papers were examined to identify relevant references that could be missed by the electronic search. Articles published before November 1998 were quoted when appropriate.

Methodology for surveys:

a. Survey of medical directors across Canada

The contacts for each Health Ministry across the country (N=12) were those who attend the provincial/territorial Medical Directors meetings, or individuals they designated to respond to this survey. An introductory letter and copy of the survey questions were faxed to each individual on June 20th, 2000, and follow-up with non-respondents was done the week of July 5th, 2000. Responses were obtained between June 22nd and July 26th, 2000, from all twelve individuals. Each individual was then sent the researcher's interpretation of their responses and asked to confirm their accuracy. As of July 28th, 2000, six of the twelve total respondents had confirmed the interpretation, including Yukon, Quebec, Ontario, Newfoundland, Saskatchewan, and Manitoba.

The survey consisted of eight questions in five specific areas (see Appendix B). The five areas addressed:

- whether vagus nerve stimulation was offered in their province or territory,
- the funding coverage of the surgical procedure,
- the funding coverage of the device and its components,
- limitations of coverage according to the specific diagnosis of epilepsy, and
- limitations of coverage according to the age of the patient.

b. Survey of manufacturers of VNS devices

A search of manufacturers of vagus nerve stimulators was conducted through a variety of sources. Articles used in the past Health Technology Technote [7] were scanned for manufacturer names. An Internet search on 'vagus nerve' and 'vagus nerve stimulation' turned up numerous web sites on anecdotal success stories, epilepsy organizations, research articles and many others. Medical Devices databases were searched, as were the FDA and Health Canada web sites.

The questions asked were in relation to:

- prices of the device and its components;
- differing costs for children and adults; and
- replacement costs for each component of the system.

APPENDIX B: QUESTIONS USED IN THE SURVEY OF MEDICAL DIRECTORS ACROSS CANADA

Thank you for taking time to talk with me about Vagus Nerve Stimulation (VNS), a therapeutic intervention for individuals with epilepsy. We are interested in Medicare coverage information regarding this procedure, for the province (territory) of _____. The questions address the surgical procedure itself, and the device used in vagus nerve stimulation, the Neuro Cybernetic Prosthesis (NCP) System. We will refer to it as the VNS device.

1. Is VNS currently offered/available as a treatment for patients with epilepsy in your province/territory?

2. Is the implantation procedure of the VNS device covered/reimbursed?

   If so, is it for an inpatient or outpatient procedure, or both?

3. Is the procedure to replace the pulse generator/batteries covered/reimbursed?

   If so, is it for an inpatient or outpatient procedure, or both?

4. How often are these procedures covered/reimbursed in an individual's lifetime? Does this vary for children and adults?

5. Is the cost of the entire VNS device covered/reimbursed?

6. If it is covered, is there a limit to how often an individual can have these components covered/reimbursed in their lifetime?

7. For what diagnoses of epilepsy is this procedure covered? Are there limitations according to types of epilepsy, that impact on the coverage of the procedure?

8. What are the age parameters that affect the coverage of these procedures, if any? For example, is there a minimum age for a child or a maximum age for an adult?

9. Any other comments.

APPENDIX C: COST ISSUES

VNS therapy as a treatment modality is not cheap. According to ECRI, the manufacturer estimates that the device costs ~9,200 USD and the cost of a generator replacement is ~ 6,900 USD [11, 12]. Direct medical costs include those for surgery, hospitalization and follow-up visits to program the device. The implantation can cost from 13,000 to 25,000 USD (including the device) [11, 12]. Optimal programming may require several physician visits over several weeks [12]. However, the average number of physician visits required has yet to be established. Battery life varies with the individual patient and costs associated with battery replacement will vary as well [12]. Additional costs include some maintenance costs.

A total 5-year cost of VNS therapy has been estimated at about £ 11,615 per patient [7]. This total included direct costs for the first 5 years of VNS therapy (work-up, device, surgery with overnight hospitalization, and follow-up/clinic visits) and costs of the following years (only those associated with outpatient/ clinic visits). By modeling the possible effects of the VNS therapy and assuming a 0.79 seizure/day and a 30% reduction in seizure frequency, it has been calculated that 86 seizures could be prevented per person per year. For every 100 patients treated, the number of seizures prevented could be 2580 if 30% of patients responded and 4300 if 50% patients responded.

Savings due to successful VNS therapy may be obtained if there is a reduction in medication, physician visits and hospital admissions [7]. It is not yet known whether VNS will enable patients to reduce AED intake and the associated costs. By decreasing seizure frequency, VNS may decrease hospital admissions due to seizures and resulting complications [12]. This may result in a net decrease in treatment cost.

Recently, Boon et al. [4] reported results of a "cost-benefit analysis" conducted on all 25 patients who received VNS at one center. They included in their analysis the first 20 patients who had sufficient follow-up (mean post-implantation follow-up of 26 months, range 6-50 months). In these patients, mean age was 30 years (range 12-45 years), mean duration of epilepsy was 17 years (range 5-35 years). Investigators prospectively assessed seizure frequency, prescribed AEDs, number of hospital admission days and side effects and calculated the epilepsy-related direct medical costs (ERDMC) and compared these data with pre-implantation data on the same outcomes. The mean evaluation time before implantation was 35 months (range 6-132 months).

The investigators chose to calculate the ERDMC using a simple algorithm, which reflects the costs of daily therapy for refractory epilepsy (costs of AEDs, costs of clinic visits, costs of hospital admissions, and costs of laboratory tests) [4]. For each individual patient, a comparison was made between the mean sum of these

costs in the years before and in the available follow-up after implantation. The total numbers of hospital admission days per year before and after procedure were also compared. The aim was to examine the cost of daily ongoing treatment of epilepsy. The costs of specific pre-surgical diagnostic examinations were not taken into account. The cost of the VNS device and the implantation procedure in Belgium is approximately $10,000 USD.

The data obtained showed that during the follow-up time after implantation the mean yearly ERDMC per patient dropped from 6,682 USD (range 829-21,888 USD) to 3,635 USD (range 684-12,486 USD) (p=0.0046). The mean number of hospital admission days was reduced from 16 days/year (range 0-60) to 4 days/year (range 0-30) (p=0.0029). The investigators suggested that in their study population "the cost of the device and the implantation procedure can be recouped by savings in ERDMC within 3 years after implantation, while battery life now exceeds 5 years". They concluded that VNS is efficacious and safe therapy for medically refractory epileptic seizures during the first year of implantation and has a "favorable cost-benefit".

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