Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Implantation of vagus nerve stimulation (VNS) in the treatment of patients with medically refractory epilepsy who are unsuitable candidates for conventional epilepsy surgery. The Neurocybernetic Prosthesis (NCP) system, which comprises a pulse generator and bipolar helical lead with an integral tether is implanted during a surgical procedure under general anaesthesia. Stimulation is initiated within 2-4 weeks after surgery. The parameters are programmed to a stimulation frequency of 30 Hz, pulse width of 500 Mius, on/off periods of 30s/300-600 ('standard stimulation’) and with the output current being turned up to individual patient tolerance, maximally 3 mA, over the weeks after implantation. The patients are provided with a magnet allowing additional stimulation to be commanded by the patient or carer in case of an aura or a seizure.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients with medically refractory epilepsy who are unsuitable candidates for conventional epilepsy surgery.

Setting
Hospital. The economic analysis was carried out in Belgium.

Dates to which data relate
Effectiveness and resource use data corresponded to patients treated between 1995 and 1999. The price year was not specified.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.

Link between effectiveness and cost data
Costing was conducted retrospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were not used to determine the sample size. In total, 25 patients were treated by VNH implantation, of whom 20 with a mean (SD) age of 30 (9.0; range: 12 - 45) years who had sufficient follow-up data comprised the study sample. The study patients had a mean (SD) duration of epilepsy of 17 years (8.0; range: 5 - 35 years). The 20
patients within the study sample were part of a population of 150 patients who underwent an extensive pre-surgical evaluation that included scalp video-EEG monitoring, optimum magnetic resonance imaging (MRI), interictal fluorodeoxyglucose positron emission tomography (FDG-PET) and neuropsychological assessment. After thorough pre-surgical evaluation, 105 of 150 patients were considered as the non-surgical candidates who were either offered continuing drug therapy with a re-matching of their standard antiepileptic drugs (AEDs) (n=50), participation in phase-3 drug trials with novel AEDs such as topiramate, gabapentin or levertiracetam (n=30), or VNS (n=25).

**Study design**
This was a before-and-after study, carried out in a single centre. The mean post-transplantation follow-up time was 26 months (range: 6 - 50 months; SD: 14.4). Patients were followed on an outpatient basis at regular intervals, usually every 2-4 weeks during ramping up and every 1 to 3 months thereafter. Loss-to-follow-up comprised 5 patients who lacked sufficient follow-up data.

**Analysis of effectiveness**
The principle used in the analysis of effectiveness was treatment completers only. The clinical outcome measures were seizure frequency, prescribed AEDs together with the dosage as well as side effects of VNS. These outcomes were assessed at every clinic visit. Seizure frequency during the two year period before the implantation was assessed by careful analysis of the clinical notes in the patient records and seizure diaries.

**Effectiveness results**
The effectiveness results were as follows:

The mean (SD) seizure frequency decreased from 14 (13.8) seizures per month (range: 2-40) in the period before implantation to 9 (12.3) seizures per month (range: 0-30) (p=0.0003) after implantation.

The mean number and dosage of AEDs remained unchanged in 14 patients after implantation. In one patient two AEDs were tapered, in one patient one AED was tapered. In 4 patients an additional AED was administered.

Regarding the side-effects of the treatment, it was reported that all patients experienced an indescribable throat sensation during the first stimulation trains, which subsided over 24 hours and was considered as an intrinsic and minor side-effect of VNS that did not cause pain or discomfort to the patient.

Hoarseness, voice change, paresthaesias in the throat or in the area around the stimulator, dysphagia and persistent coughing during stimulation were reported in 10 patients during ramping-up.

In three patients these side-effects required a temporary reduction of output current but in none of the patients did stimulation have to be interrupted.

Six patients reported side effects at the time of maximum follow-up. These side effects did not require any change of stimulation output and subsided over time.

**Clinical conclusions**
The study experience confirms the efficacy rate (50% reduction in seizure frequency in about 25% of patients) observed in the literature which compares favourably with new AEDs such as lamotrigin, topiramate, and gabapentin. Results in the study population in Belgium suggest that VNS remains effective in the long-term. Most acute side-effects are related to initial stimulation and resolve spontaneously without the need to stop the stimulation.

**Measure of benefits used in the economic analysis**
No summary benefit measure was identified in the economic analysis, and only separate clinical outcomes were reported.
Direct costs
Costs were not discounted due to the short time frame of the cost analysis. Some resource use quantities were reported separately from the costs. Cost items were reported separately. Cost analysis covered the costs of AEDs, clinic visits, hospital admissions, laboratory tests, and the VNS stimulator and the implantation procedure. The yearly cost of clinic visits was calculated in the years prior to implantation and during the follow-up time after implantation. The perspective adopted in the cost analysis was not explicitly specified. The costs for the period before and after implantation were calculated on a per patient basis. The source of cost data was the study institution. The price year was not specified. The cost analysis did not cover the costs associated with hospital admissions due to conditions unrelated to epilepsy or epileptic seizures and admissions scheduled solely in the context of the pre-surgical evaluation.

Statistical analysis of costs
The paired student's t-test was used for statistical analysis.

Indirect Costs
Not included.

Currency
US dollars ($).

Sensitivity analysis
Not conducted.

Estimated benefits used in the economic analysis
Not applicable.

Cost results
The mean yearly epilepsy related direct medical costs per patient dropped from $6,682 (range: $829 - $21,888) in the period before implantation to $3,635 (range: $684 - $12,486) (p=0.0046), after the VNS implantation.

Synthesis of costs and benefits
Costs and benefits were not combined since the use of the intervention procedure (VNS implantation) was the dominant strategy.

Authors' conclusions
VNS is an efficacious and safe treatment for medically refractory epileptic seizures during the first years after implantation. It appears to be equally effective and safe in the long-term and lacks the common side effects of AEDs. VNS has a favourable cost-benefit.

CRD COMMENTARY - Selection of comparators
The strategy of not using VNS (in the period before VNS implantation) was explicitly regarded as the comparator, which allowed the active value of the VNS implantation to be evaluated. You, as a database user, should consider whether this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness results is not as strong as it could be due to the potential for various types of bias and confounders in the before-and-after study design and the small sample size. The study sample appears to have been representative of the study population.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit. The study was therefore a cost-consequences analysis.

Validity of estimate of costs
Good features of the cost analysis were that: some resource use quantities were reported separately from the costs; adequate details of methods of cost estimation were given; and statistical analyses were performed on resource use and cost data. However, price years and the perspective adopted in the cost analysis were not reported. It appears that the equipment cost should have been discounted since the costs were calculated on a yearly basis and the equipment had a working life of more than 1 year. The limitations were that: the effects of alternative procedures on indirect costs were not addressed and the cost results may not be generalisable outside the study settings.

Other issues
Given the above limitations, the study results should be treated with some degree of caution. The issue of generalisability to other settings or countries was not addressed, although appropriate comparisons were made with other studies. The degree to which the study sample was representative of the study population was not discussed.

Implications of the study
The main issue in further establishing the clinical efficacy of VNS is to determine whether there are specific types of epileptic seizures or epileptic syndromes that respond better to VNS and how different stimulation parameters influence clinical response. More information on efficacy and safety in larger patient series is needed.

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