NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of vagus nerve stimulation for refractory epilepsy in children

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in June 2003.

Procedure name

Vagus nerve stimulation (VNS).
Vagal nerve stimulation.

Specialty societies

Specialist advice was sought from:

British Association of Paediatric Surgeons.
Society of British Neurological Surgeons.

Description

Indications

Epilepsy prevalence is 2% to 5% worldwide (World Health Organisation estimate) and represents one of the most common neurological problems affecting children.

Epilepsy is caused by a brief disruption of brain function involving temporary abnormal electrical activity in the nerve cells. Where this activity occurs determines the type of seizure. The two main types of seizures are partial (involving part of the brain) and generalised (whole brain). Partial seizures can become generalised over time. The type of seizure determines medical treatment.

About 5% to 30% of people with epilepsy have medically refractory complex partial seizures.

There are also some childhood epilepsy syndromes, such as Lennox-Gastaut Syndrome (LGS), that are typically resistant to anti-epileptic drugs. LGS accounts for around 3% to 11% per cent of childhood epilepsies. It usually develops during preschool years and is characterised by the presence of several seizure types and cognitive impairment.

Current treatments and alternatives

For the majority of people with epilepsy treatment consists of anti-epileptic drugs (AEDs) given either singly or in combination. However, a significant proportion of people with epilepsy continue to have seizures. When this occurs, it is referred to as refractory or intractable epilepsy.

Drug therapy is therefore, by definition, not an alternative for children with medically refractory epilepsy. However, the criteria for deciding whether a child is responding or refractory to medical therapy may vary among practitioners. In these cases neurosurgery, such as lobectomy or callosotomy, may be considered as an option. Recently there has also been increased interest in the ketogenic diet [1-2]

VNS is indicated for use as an adjunctive therapy to reduce the frequency of seizures in patients whose epileptic disorder is dominated by partial or generalised seizures that are refractory to anti-epileptic medication.

What the procedure involves

A battery-powered pulse generator device is implanted under the skin of the upper left chest. A wire is tunnelled under the skin and connected to the left vagus nerve in the neck. Stimulation parameters (pulse width and frequency, current intensity, and on/off cycles) are programmed into the pulse generator via a programming wand.

Patients or carers can give additional stimulation or temporarily inhibit stimulation by activating a switch with a magnet.

The battery for the current device (Model 101) lasts 8–10 years and can be replaced under local anaesthetic. A typical treatment regimen might comprise intermittent stimulation for 30 seconds every 5 minutes throughout the day and night.

Efficacy

- In one study that included 50 children younger than 12 years of age, 46% experienced a more than 50% reduction in seizure frequency at their most recent visit. In a smaller study of 28 children younger than 12 years of age a mean reduction of 62% was reported in seizure frequency at 1 year.
- There was also evidence to suggest that quality of life improved as a result of the procedure. In one study 48% of patients or carers thought that alertness was better or much better after 3 months.
- It is difficult to make comparisons among the studies because of the varied patient population, reporting of outcomes and method of outcome assessment.
- The quality of the evidence in patients with LGS is poorer. In the largest study on this patient population median reduction in total seizures was 58% at 6 months. There were also some data to suggest that patients with higher levels of function had greater improvement.
- The Specialist Advisors agreed that approximately 50% of patients having this procedure had a reduction in seizure frequency of around 50%. One Specialist Advisor believed that these figures were true for adults, and although the outcomes seemed similar in children not enough data had been published. Two Advisors also noted that the procedure had benefits in terms of mood and quality of life.

Safety

- The most commonly reported complications were hoarseness, sore throat and cough. In a case series of 125 children 58% and 38% experienced voice alteration and coughing after the procedure. These complications were mainly of a transient nature and occurred during stimulation. More serious adverse events included infection (requiring device removal) and breathing irregularities but these occurred in a small number of cases.
- The Specialist Advisors considered that this is a safe procedure with no major complications. Potential minor adverse events were listed as hoarseness, throat irritation and infection.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to VNS in children with refractory epilepsy. Searches were conducted using the following databases: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index, and covered the period from their commencement to June 2003. Trial registries and the Internet were also searched. No language restriction was applied to the searches. The search strategy was based on the Cochrane Epilepsy Group search strategy.

The following selection criteria (Table1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Evidence was considered in order of level, quality and strength. Abstracts were excluded where no clinical outcomes were reported, or the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Children with refractory epilepsy.
Intervention/test	Vagus nerve stimulation.
Outcome	Articles were retrieved if the abstract contained information relevant to safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

Results of the literature search

The literature search identified 273 non-duplicate abstracts on VNS for refractory epilepsy in children. A total of 43 full text articles were retrieved. Twelve of these were excluded, as they did not report relevant and/or adequate information on a paediatric population.

Review papers were also excluded, although four papers were retrieved for background information as they specifically addressed the question of VNS in a paediatric population [3-6]. Three papers analysing the results of the VNUS registry were also retrieved for background information although excluded from the data extraction process [7-9].

This overview is based on nine studies, including three papers on LGS. Papers that met the inclusion criteria but were not included in this overview are listed in Appendix A (15 papers).

Existing reviews on vagus nerve stimulation

Two systematic reviews of VNS were identified. An outline of the included studies and conclusions of these reviews are presented below.

Cochrane review: Vagus nerve stimulation for partial seizures

Search date 2000.

The Cochrane reviewed included two randomised double-blind controlled trials of vagus nerve stimulation comparing high and low stimulation paradigms. A total of 312 patients were included in these studies. The mean age of patients in the studies was approximately 33 years. A subgroup analysis on age was not performed.

The review concluded that VNS appeared to be an effective treatment for the adjunctive treatment of medication-resistant partial seizures. However, the results cannot be extrapolated to other patient groups such as children under the age of 12 years with generalised epilepsy.

Alberta Heritage Foundation for Medical Research: Vagus nerve stimulation for refractory epilepsy.

Search date 2001 (update)

Evidence in the review was divided into four sections: follow-up on VNS in patients with refractory epilepsy; VNS in children with refractory epilepsy; VNS for patients with LGS; VNS in generalised epilepsy.

VNS in patients with refractory epilepsy

The evidence on VNS in children with refractory epilepsy was based on five studies. Three of these studies were reported on in the earlier review [10-12] and two were included in the updated report [13-14]. All studies were uncontrolled.

VNS for patients with LGS

The evidence on VNS in children with LGS is based on two papers [15-16] one of which was a review paper that pooled and discussed the results of VNS for 28 children from five separate studies [15].

The report concluded that the reviewed literature suggests that VNS therapy is safe, well tolerated and effective when used as adjunctive therapy in patients (older than 12 years of age) with partial-onset seizures refractory to medication, who are not candidates for epilepsy surgery or for whom surgery has failed.

Table 2 Summary of key efficacy and safety findings in studies of vagus nerve stimulation for refractory epilepsy

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key reliability and validity issues
Helmers SL (2001) [17] uncontrolled study Six centres: Boston, Houston, Denver, Minnesota, New Orleans, Washington; USA. Implanted 1997 to December 1998, follow-up to March 1999. 125 children with RE, (median age 12 years, range 3–18 years; 41 children <12 years) Seizure types: • partial (n = 59) • generalised seizures (n = 23) • LGS (n = 43; see Frost [2001] below for analysis of these patients) 35 children had previous surgery: • lobectomy (13) • callosotomy (18); • both (2) Children had tried a mean of 8.6 (range 2–17) different anticonvulsants before VNS. Children were taking a mean of 2.3 anticonvulsants at time of implant (range 1–5) Follow up: • 3 months (n = 95) • 6 months (n = 56) • 9 months (n = 12)	**Seizure frequency** At 3 months (n = 95), mean seizure frequency reduced by: • 36% from baseline for all groups (p < 0.0001) (range –100 to +312%) • 27% for LG subgroup • 25–32% for other subgroups • 18% in children < 12 years (n = 41) At 6 months (n = 56), mean seizure frequency reduced by 45% (p < 0.0001). Similar reduction for children < 12 years 46% (n = 20) **Medication use** • 3 months: anticonvulsant use decreased in 10/95 (11%), unchanged in 65/95 (68%) • 6 months -anticonvulsant use decreased in 9/56 (16%), unchanged in 33/56 (59%) **Quality of life (QOL)** At 3 months, quality of life measures reported by patients or carers as 'better' or 'much better' for: • alertness 46/96 (48%) • seizure clustering 34/96 (36%) • verbal communication in postictal periods 26/96 (27%) • school achievements and mood 21/96 (22%) • memory in 13/96 (14%) • ambulation 5/96 (5%)	**Complications** • 58% voice alteration during stimulation • 38% coughing during stimulation • 1% ear pain • < 1% increased drooling – resolved spontaneously • 'few' children increased hyperactivity • 1 patient left vocal cord paralysis causing moderate to severe dysphonia – 'almost completely' resolved at 4 months • 1 patient right sided weakness, incoordination requiring 3 emergency visits – resolved spontaneously • 3 patients broken electrode leads No explants, no deaths, no status epilepticus	Retrospective Follow-up not available for 30 patients at 3 months and 69 patients at 6 months. Accuracy of reports of seizures depended on records by carers and patients.

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key reliability and validity issues
Murphy (2003) [18] Retrospective uncontrolled Kansas City, USA. 100 patients with RE (mean age at implant 10.4 years, range 2–40 years) 50 children ≤ 12 years. 34 children 12–18 years 12 children 18+ years First patient underwent implantation November 1992 – last July 2000. Follow up: 1–9 years (mean 2.7 years) 12 patients had 1 year follow up	**Seizure frequency**: Compares the frequency during the month before the most recent visit with the monthly average 3 months before implantation. **Response** / **≤ 12 years** / **12–18 years** / **CI %** No seizures 10 (20%) 7 (21%) -17 to + 20% > 90% reduction 14 (28%) 10 (29%) -18 to + 22% > 50% reduction 23 (46%) 16 (47%) -21 to + 22% All patients: 45% of patients experienced > 50% reduction, 18% had no seizures for last 6 months. Five patients (1 patient 12–18 years; 3 patients < 12 years) had increased seizure frequency – increases of 11–150%. Four of these five had no improvement in well-being. **Removal of device – no age breakdown** 24/96 patients (25%) had device removed 1 patient for cosmetic reasons (at 3 months) 23 patients because of lack of efficacy (after at least 18 months) **Use of other therapies** Average number of antiepileptic therapies at the time of implantation was 2.23. At the time of review the number was 2.00. **Well-being** (measured at last evaluation n = 68) Unclear how this was measured. No age breakdown. Much better 32/68 (47%) Better 10/68 (15%) No change 24/68 (35%) Worse 2/68 (3%) Authors report no correlation with seizure control	**Complications** • 3 patients abscesses around generator requiring removal and re-implantation • 1 patient voice change with stimulation	Retrospective 4/100 lost to follow up • 1 family refused follow up • 2 physicians didn't forward data • 1 family could not be located Unclear the age group of children lost to follow-up. Measurement tool for well-being is unclear. More than one surgeon implanted the device. Unclear whether categories are inclusive. First 28 patients had their treatment paid for by the manufacturer of the device.

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key reliability and validity issues
Patwardhan et al (2000) [19] US uncontrolled 38 consecutive patients with refractory epilepsy Implantation occurred during a 14 month period Age range 11 months to 17 years (median 8 years) Seizure type (20 children,some with more than one type) • Atonic 17 • Generalised 23 • Absence 17 • Complex partial 11 Inclusion criteria stated Factors looked at included • Age at implantation • Age of seizure onset • Epilepsy duration • Follow up Follow-up: 10–18 months (median 12 months)	**Seizure frequency**: at a median follow up of 12 months. **Response** **Number of children** > 90% reduction 11 (29%) 50–90% reduction 15 (39%) < 50% reduction 5 (13%) No reduction 7(18%) **Age at implant** **Number** **Reduction (%)** ≤ 12 years 28 62% > 12 years 10 77% All 38 66% Patients with atonic seizures received the greatest reduction. **Quality of life**: Visual analogue scale –1 (much worse) to +1 much improved **Age at implant** **Number** **QOL** ≤ 12 years 28 0.63 > 12 years 10 0.61 **Follow up (by reduction and QOL)** **Follow up** **Reduction%** **QOL** < 6 months 52 0.44 ≥ 6 months 70 0.76 < 12 months 62 0.65 ≥ 12 months 72 0.78	**Complications** • 20 patients (54.3%) hoarseness (transient, when stimulator on) • 5 patients (14.3%) cough (transient when stimulator on) • 3 patients (8.6%) dysphasia (mild transient) • 1 patient (2.9%) infection (removal of device) • 1 patient (2.9%) dysautonomia • 1 patients (2.9%) raises left arm (when stimulator on)	Retrospective Adverse events and QOL measured by carers – data obtained at visit/telephone interview. Two neurologists involved with follow-up so may have been differences in management. Authors suggested that stimulation parameters changed throughout study.

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key reliability and validity issues
Nagarajan et al (2002) [20] Australia uncontrolled 16 children with refractory epilepsy All had a degree of cognitive disability • 12 children <12 years. • 4 children 12-18 years Age range at implantation 9.6 years (range 3–17 years) Seizure type varied in patients Patients receiving a mean of 2.5 AEDs at implantation. Follow up: 6–47 months (mean 24.9, median, 25)	**Seizure frequency**: Compares the frequency during the month before the most recent visit with the monthly average 4 months before implantation. **Response** **No < 12 years** **No of children** > 90% reduction 3 (25%) 4 (25%) 50–90% reduction 3 (25%) 6 (37.5%) < 50% reduction 3 (25%) 3 (19%) No reduction 2 (17%) 2 (12.5%) Seizures increased 1 (8%) 1 (6%) **Total** **12** **16** In children < 12 years (n = 12): 7 had a reduction in severity. In all children (n = 16): 10 had a reduction in severity. Authors note that in three children the initial response was not sustained. **Medication use** Unchanged **QOL (3 point scale)** (n = 16) • 12 parents reported quality of life was better • 12 children had better behaviour, 2 it had worsened • 11 children changed sleep, 5 had improved sleep • 15 alertness and awareness were increased • 10 language had improved	**Complications** Authors noted that no serious complications in our study • 2 families reported transient choking episodes • 1 patient sore throat • 3 patients hoarseness • 1 patient tingling, paraesthesias, vertigo • 1 patient increase in drooling • 4 patients weight loss • 3 families reported breathing irregularities • coughing (transient)	Retrospective Authors suggested that stimulation parameters changed throughout study. Carers reported complications QOL. Unsure what questions were asked in relation to QOL.

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key reliability and validity issues
Parker et al (1999) [14] UK uncontrolled 1995–1996 16 children with epileptic encephalopathies 10 children developed/had LGS Mean age at implant 11 years 1 month (range 5–16 years) 12 children used > 7 AEDs before implant 4 children used 3–6 AEDs before implant Follow up: 12 months	**Seizure frequency**: recorded for at least at 8 week baseline period and for 1 year after (diary) **6 months** all children 19% reduction compared with baseline (p = 0.83) 2/16 (12.5%) children > 50% reduction 2/16 (12.5%) children > 50% increase **6-12 months** all children 17% reduction compared with baseline (p = 0.264) • 4/16 (25%) children > 50% reduction • 2/16 (12.5%) children > 50% increase **EEG** (9 children) No improvement in the background, focal or generalised discharges **Adaptive behaviour (Vineland adaptive behaviour scale)** No different in communication, living, socialisation domains **QOL (Wellcome QOL assessment)** Significant improvement in perceived treatment side effects and general behaviour. No correlation between changes in these domains and seizure frequency **Verbal/nonverbal performance, behaviours and hyperactivity** (6 children – Vineland, Conners questionnaire Leiter scale) **Addendum** (15 patients – excluding one who had device removed) – 2 years' follow up **Seizure frequency (average of absolute seizure number)** Median percentage reduction 43% • 1 patient seizure free • 5 patients > 60% seizure reduction • 3 patients > 40% reduction No patient is experiencing more seizures than before the implant. All but 2 families are pleased that they underwent treatment	**Complications** 1 patient infection (device removed)	Prospective Validated outcomes measures. Caregivers asked to fill in QOL forms. Longer baseline period (8 weeks) in an attempt to reduce placebo effect. Discrepancy between parents' response to the single question on their children's QOL and the results of the more comprehensive questions. Carers were requested not to change antiepileptic medication during the trial. Authors note possible bias with addendum results as some patients had changed medication regime, changed current.

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key reliability and validity issues
Lundgren et al (1998) [11] Sweden uncontrolled 16 children intractable epilepsy (7 had surgery) Mean age at implant 11 years (range 4–19 years) • 11 children < 12 years • 5 children 12–19 years Majority of children had a cognitive impairment. Seizure type • 8 partial • 8 generalised • 4 LGS Patients received one to three antiepileptic drugs (AEDs) with no changes during the 6 months. NCP Model 100 Follow up: 4–24 months	**Seizure frequency**: (compared with baseline measurements from diary) **Follow up 10–12 months** **Response** / **No** / **< 12 years** / **All children** > 50% reduction: 4 (36%) / 6 (38%) < 50% reduction: 4 (36%) / 5 (31%) No change: 2 (18%) / 2 (12.5%) Increase < 50%: 0 / 1 (6%) Increase > 50%: 1 (9%) / 2 (12.5%) **Total**: **11** / **16** Follow-up 11 patients 16–8 months; 2 patients 22–4 months 5 patients discontinued treatment after 9–20 months because of lack of efficacy **QOL at 10–2 months** (visual analogue scale –100 considerably worse, 0 no change, +100 considerable improvement) **Patients < 12 years**: 4 patients 50–100; 4 patients 0–50; 3 patients 0 **All patients**: 6 patients 50–100; 6 patients 0–50; 4 patients 0	**Complications** • 6 patients hoarseness (transient) • 1 patient throat pain • 2 patients increased salivation • 2 patients tiredness • 2 patients aspiration (one partly transient) • 1 severe fibrosis • 1 electrical line fracture • 5 premature failure	Unclear when baseline measurements taken and over how long. NNH3 score also given. Quality of life visual analogue scale 1 patient AED medication was changed

Table 3 Summary of key efficacy and safety findings in studies of vagus nerve stimulation in children with Lennox-Gastaut Syndrome

Authors, location, date, patients					Key efficacy findings	Key safety findings	Key reliability and validity issues
Karceski, S (2001) [21], Labar, D (2000) [15] Narrative review papers. Papers do not explicitly describe search criteria.	**Authors** Ben-Menachem[23] Horning [10] Hosain [16] Lundgren [11] Parker [14] Labar [24]	**No. LGS** 8/64 6/19 13/13 4/16 10/16 5	**Age** Not known 6–16 years 4–44 years 4–19 years 6–16 years 23–44 years	**Follow up** Mean: 20 months 2–30 months > 6 months Mean 16 months 6–12 months 9 months	**Seizure reduction** 62% LGS patients had >50% (0 to –100) 83% LGS patients had > 90% reduction 53% reduction 37% of patients had 50% reduction Median 34% in patients with LGS at 12 months 58% reduction (range: 28–93%)	Safety is not systemically addressed	Search date is not documented. The paper by Labar et al (2000) [15] is referred to in the HTA on this topic. Both reviews note the difficulty in generalising results.
	Although both reviews included a number of similar papers the data presented do not always reconcile.						

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key reliability and validity issues
Frost, M (2001)[25] Retrospective uncontrolled study Kansas City, USA. Six centres: Boston, Houston, Denver, Minnesota, New Orleans, Washington; USA. Implanted 1997 to December 1998, follow-up to March 1999 N = 50 children with LGS (median age 13 years, range 5–27 years; 21 patients < 12 years at implant) • 6 children had previous surgery: lobectomy (1) • callosotomy (5) Follow up: • 1 month (n = 46) • 3 months (n = 43) 6 months (n = 24)	**Seizure frequency** Median number of seizures reduced by: • 42% at 1 month • 58% at 3 months • 58% at 6 months ($p < 0.0001$ for all comparisons with baseline) Quality of life improved for 'some' patients in study (no numbers stated) No patients seizure free after treatment	**Complications** • Seizures increased by 50% in 1/46 patients at 1 month; 3/43 patients at 3 months • 2 patients wound infections at incision site • 5 patients transient pain at incision site • 22 patients voice alteration • 15 patients coughing • 4 patients paraesthesia during stimulation • 2 patients exertional dyspnoea • 2 patients decreased appetite • 2 patients hiccups • 2 patients dyspepsia • 1 patient dysphagia • 1 patient vomiting • 4 patients increased drooling – 3 patients resolved after altering medication and stimulation • 2 patients quality of life reported as 'worse'	Note: included same patients as Helmers [17] but analysis specific to LGS patients. Drop out: four at 1 month (because of inadequate recording of information). Declining number of patients with time due to date cut off of study. Quality of life data presented graphically; no absolute figures reported.

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key reliability and validity issues
Aldenkamp et al (2002))[26] Netherlands Uncontrolled study 19 children with LSG or LSG-like syndromes (5 patients) Mean age 11.2 years, age range 6.3–19.8 years Inclusion criteria clearly stated All children had multiple seizure type. Most patients (16) on 2–4 AEDs Follow up: 6–24 months • 6 months 19 patients • 12 months 18 patients • 24 months 17 patients	**All patients were assessed at baseline then at 6, 12, 18 and 24 months.** **Seizure frequency** **Mean** **Reduction %** Baseline 167.6 6 months 134.1 20% 12 months 125.6 25% 18 months 156.2 7% 24 months 133.0 21% **No.Patients** **Seizure reduction** **Mental age** 4 > 50% reduction 89.3 months 7 < 50% reduction 15.0 months 6 no reduction 20.3 months Positive effects in patients with highest level of function **Cognition standard deviation (SD)** **Mean mental age (months)** Baseline 30.2 (40.5) 6 months 32.8 (45.4) 12 months 33.2 (50.6) 18 months 33.2 (49.6) 24 months 34.4 (52.8) **Quality of life (Dutch scales) standard deviation (SD)** SRZ: scale 3–9 independence (where 9 is good improvement) SGZ: scale 3-9 behaviour (where 9 is good improvement) TVZ: scale 1 – 10 (where 10 represents good improvement) **Mean(SD) Independency (SRZ) Behaviour (SGZ) Mood (TVZ)** Baseline 3.6 (1.4) 6.6 (1.8) 7.3 (2.9) 6 months 3.4 (1.6) 6.9 (2.0) 7.4 (3.5) 12 months 3.2 (1.1) 7.0 (2.0) 7.0 (3.3) 18 months 3.1 (1.1) 6.9 (1.8) 7.7 (2.6) 24 months 3.3 (1.0) 7.3 (1.8) 7.3 (3.0)	Authors do not address safety in the article	Lost to follow-up: • 1 patient excluded because of failure of equipment (6 months) • 1 patient withdrew consent. Objective and validated instruments to evaluate quality of life, cognition. Authors noted that minor changes were carried out during the study.

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key reliability and validity issues
Karceski, S (2001) [21] Retrospective review of the VNS patient registry uncontrolled Data collected prior to 30 April 2001 Patients with LGS (552) • naïve to surgery (483) • those who had undergone surgery (69) Time points 3, 6, 12, 18 months post implant.	**Seizure frequency – naïve to surgery** • 3 months 149/297 patients had ≥ 50% reduction in seizures • 6 months 91/160 patients were responders • 12 months 94/145 were responders • 18 months 74/74 were responders **Seizure frequency – undergone surgery** • 3 months 25/44 were responders • 12 months 13/23 were responders	No safety data were reported	Database held by manufacturer. Authors note potential bias in database – lost to follow-up; incomplete registration.

Validity and generalisability of the studies

- The primary outcome used to measure efficacy in the studies was a change in seizure frequency. This was expressed as the percentage change in seizure frequency after implantation compared with baseline as reported in caregivers diaries. As caregivers may vary in detecting and reporting seizures this method of assessment could result in an under- or over-estimate of the outcome.
- The number of patients achieving at least a 50% reduction in seizure frequency is a well-recognised measure of efficacy in epilepsy. Despite this, reporting of outcomes varied among studies. This can make interpretation and comparisons of results difficult.
- In the majority of the studies quality of life (QOL) was assessed using a visual analogue scale completed by caregivers to assess overall QOL. In only one study [14] was a validated tool used to assess QOL.
- Many of the studies included children of different ages. In one study based at a paediatric epilepsy centre, age at implant ranged from 2- 40 years [18]. Most studies reported results for children older or younger than 12 years, however this was not always the case.
- Studies also included children with a variety of different epilepsy syndromes. This makes generalising of results difficult and has implications for defining the patient population that would most benefit from this procedure.
- Follow-up varied between the studies and was not consistently or well reported. In many of the papers outcomes were measured at the 'most recent visit'. While median follow-up is reported, it is often unclear at what time point outcomes have been measured.
- The lack of controlled data makes it difficult to make assumptions about the placebo effect of the procedure [17].
- Some of the authors noted that stimulation or medication varied during the study period [19] [20] [14] [11] [25].

Specialist Advisors' opinions

- A major difficultly is in clearly recognising patients who would benefit most from the procedure.
- Manufacturer maintains a registry.
- This is a highly-specialised procedure because of the need for a highly-specialist paediatric epilepsy surgery team.
- Most patients in the UK who undergo the procedure have severe intractable epilepsy and have failed all other treatments.

Issues for consideration by IPAC

None.

References

1 Sheth RD, Stafstrom CE. Intractable pediatric epilepsy: vagal nerve stimulation and the ketogenic diet. *Neurologic Clinics* 2002; 20(4):1183-1194.

2 Wheless JW, Baumgartner J, Ghanbari C. Vagus nerve stimulation and the ketogenic diet. *Neurologic Clinics* 2001; 19(2):371-407.

3 Crumrine PK. Vagal nerve stimulation in children. *Seminars in Pediatric Neurology* 2000; 7(3):216-223.

4 Amar AP, Levy ML, McComb JG, Apuzzo ML. Vagus nerve stimulation for control of intractable seizures in childhood. *Pediatric Neurosurgery* 2001; 34(4):218-223.

5 Valencia I, Holder DL, Helmers SL, Madsen JR, Riviello JJ, Jr. Vagus nerve stimulation in pediatric epilepsy: a review. *Pediatric Neurology* 2001; 25(5):368-376.

6. Buchhalter JR, Jarrar RG. Therapeutics in pediatric epilepsy, Part 2: Epilepsy surgery and vagus nerve stimulation. *Mayo Clinic Proceedings* 2003; 78(3):371-378.

7 Wheless JW, Maggio V. Vagus nerve stimulation therapy in patients younger than 18 years. *Neurology* 2002; 59(6 Suppl 4):S21-S25.

8 Renfroe JB, Wheless JW. Earlier use of adjunctive vagus nerve stimulation therapy for refractory epilepsy. *Neurology* 2002; 59(6 Suppl 4):S26-S30.

9 Nakama H, Ohtomo S, Otsuki T, Kaneko Y, Ohnishi T, Matsuda H. Visual activation positron emission tomography for presurgical evaluation of occipital lobe epilepsy: Case report. *Neurologia Medico-Chirurgica* 2002; 42(8):356-360.

10 Hornig GW, Murphy JV, Schallert G, Tilton C. Left vagus nerve stimulation in children with refractory epilepsy: an update. *Southern Medical Journal* 1997; 90(5):484-488.

11 Lundgren J, Amark P, Blennow G, Stromblad LG, Wallstedt L. Vagus nerve stimulation in 16 children with refractory epilepsy. *Epilepsia* 1998; 39(8):809-813.

12 Murphy JV, Hornig G, Schallert G. Left vagal nerve stimulation in children with refractory epilepsy: preliminary observations. *Annals of Neurology* 1995; 52(886):889.

13 Murphy JV. Left vagal nerve stimulation in children with medically refractory epilepsy. The Pediatric VNS Study Group. *Journal of Pediatrics* 1999; 134(5):563-566.

14 Parker AP PCBCM. Vagal nerve stimulation in epileptic encephalopathies. *Pediatrics* Issue 103, pp 778-82, 1999.

15 Labar D. Vagus nerve stimulation for intractable epilepsy in children. *Developmental Medicine & Child Neurology 2000;* 42(7):496-499.

16 Hosain S, Nikalov B, Harden C, Li M, Fraser R, Labar D. Vagus nerve stimulation treatment for Lennox-Gastaut syndrome. *Journal of Child Neurology* 2000; 15(8):509-512.

17 Helmers SL, Wheless JW, Frost M, Gates J, Levisohn P, Tardo C et al. Vagus nerve stimulation therapy in pediatric patients with refractory epilepsy: retrospective study. *Journal of Child Neurology* 2001; 16(11):843-848.

18 Murphy JV, Torkelson R, Dowler I, Simon S, Hudson S. Vagal nerve stimulation in refractory epilepsy: The first 100 patients receiving vagal nerve stimulation at a pediatric epilepsy center. *Archives of Pediatrics & Adolescent Medicine* 2003; 157(6):560-564.

19 Patwardhan RV, Stong B, Bebin EM, Mathisen J, Grabb PA. Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. *Neurosurgery 2000;* 47(6):1353-1357.

20 Nagarajan L, Walsh P, Gregory P, Lee M. VNS therapy in clinical practice in children with refractory epilepsy. Acta Neurologica Scandinavica 2002; 105(1):13-17.

21 Karceski S. Vagus nerve stimulation and Lennox-Gastaut Syndrome: a review of the literature and data from the VNS patient registry. CNS Spectrums 2001; 6(9):766-770.

22 Labar D, Murphy J, Tecoma E, Sala D, Burgerman R, Gilmartin R et al. Vagus nerve stimulation for medication-resistant generalized epilepsy. Neurology 1999; 52(7):1510-1512.

23 Ben Menachem E, Hellstrom K, Waldton C, Augustinsson L. Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years. Neurology 1999; 52(6):1265-1267.

24 Labar D, Nikolov B, Tarver B, Fraser R. VNS for symptomatic generalised epilepsy. *Epilepsia* 1998; 39:201-5.

25 Frost M, Gates J, Helmers SL, Wheless JW, Levisohn P, Tardo C et al. Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. *Epilepsia* 2001; 42(9):1148-1152.

26 Aldenkamp AP, Majoie HJM, Berfelo MW, Evers SMAA, Kessels AGH, Renier WO et al. Long-term effects of 24-month treatment with vagus nerve stimulation on behaviour in children with Lennox-Gastaut syndrome. Epilepsy & Behavior 2002; 3(5 I):475-479.

Appendix A: references for relevant studies excluded from summary table

Reference	Number of children
Labar D, Murphy J, Tecoma E. Vagus nerve stimulation for medication-resistant generalized epilepsy. E04 VNS Study Group. *Neurology* 1999; 52(7):1510-1512.	24
Parker APJ, Polkey CE, Robison RO. Vagal nerve stimulation in the epileptic encephalopathies: 3-Year follow-up. *Pediatrics* 2001; 108(1):221.	9
Tatum WO, Johnson KD, Goff S, Ferreira JA, Vale FL. Vagus nerve stimulation and drug reduction. *Neurology 2001;* 56(4):561-563.	9
Murphy JV, Hornig GW, Schallert GS, Tilton CL. Adverse events in children receiving intermittent left vagal nerve stimulation. *Pediatr Neurol* 1998; 19(1):42-44.	24
Zamponi N, Rychlicki F, Cardinali C, Luchetti A, Trignani R, Ducati A. Intermittent vagal nerve stimulation in paediatric patients: 1-year follow-up. Childs Nerv Syst 2002; 18(1-2):61-66.	19
Murphy JV, Hornig G, Schallert G. Left vagal nerve stimulation in children with medically refractory epilepsy. *Journal of Pediatrics* 1999; 134(5):562-566.	60 (3-18 years)
Farooqui S, Boswell W, Hemphill JM, Pearlman E. Vagus nerve stimulation in pediatric patients with intractable epilepsy: case series and operative technique. *Am Surg* 2001; 67(2):119-121.	6 (7-18 years)
Wakai S, Kotagal P. Vagus nerve stimulation for children and adolescents with intractable epilepsies. *Pediatr Int* 2001; 43(1):61-65.	5 (3-19 years)
Shih JJ, Devier D, Behr A. Late onset laryngeal and facial pain in previously asymptomatic vagus nerve stimulation patients. *Neurology* 2003; 60(7):1214.	2
Kirse DJ, Werle AH, Murphy JV, Eyen TP, Bruegger DE, Hornig GW et al. Vagus nerve stimulator implantation in children. *Archives of Otolaryngology -- Head & Neck Surgery* 2002; 128(11):1263-1268.	102 (21 mths – 40 years)
Zalvan C, Sulica L, Wolf S, Cohen J, Gonzalez-Yanes O, Blitzer A. Laryngopharyngeal dysfunction from the implant vagal nerve stimulator. *Laryngoscope 2003;* 113(2):221-225.	2 (< 12 years)
Schallert G, Foster J, Lindquist N, Murphy JV. Chronic stimulation of the left vagal nerve in children: effect on swallowing. *Epilepsia 1998;* 39(10):1113-1114.	8
Lundgren J, Ekberg O, Olsson R. Aspiration: a potential complication to vagus nerve stimulation. *Epilepsia* 1998; 39(9):998-1000.	7 (4-18 years)
Tanganelli P, Ferrero S, Colotto P, Regesta G. Vagus nerve stimulation for treatment of medically intractable seizures. Evaluation of long-term outcome. *Clinical Neurology & Neurosurgery* 2002; 105(1):9-13.	4 (< 12years)
Parain D, Penniello MJ, Berquen P, Delangre T, Billard C, Murphy JV. Vagal nerve stimulation in tuberous sclerosis complex patients. *Pediatric Neurology* 2001; 25(3):213-216.	4 (< 12 years)