Vagus nerve stimulation for epilepsy

June 2008

MSAC application 1118

Assessment report

ISBN: 1-74186-747-9
Online ISBN: 1-74186-748-7

ISSN (print) 1443-7120

ISSN (online) 1443-7139

First printed November 2008

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's internet site at http://www.msac.gov.au/

Printed copies of the report can be obtained from:

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Ms Liz Buckley, Ms Tracy Merlin and Professor Janet Hiller from Adelaide Health Technology Assessment. The report was edited by Ms Jo Mason, MasonEdit, South Australia This recommendation was endorsed by the Minister for Health and Ageing on 28 August, 2008

Publication approval number: P3-4563

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Epilepsy is characterised by repeated and unprovoked seizures. Seizures may arise from many different regions of the brain and are caused by excessive neuronal activity. The condition where seizures are not controlled by anti-epileptic drugs (AEDs) is known as medically refractory epilepsy.

Vagus nerve stimulation (VNS) therapy provides repeated electrical stimulation to the left vagus nerve with the aim of preventing seizures. The device, which is similar to a pacemaker in appearance, is implanted in the upper chest and electrodes are attached to the vagus nerve in the neck. The procedure itself is relatively simple and does not require specialised medical equipment (other than the device itself). Due to the unstable nature of epilepsy in patients for whom this therapy may be appropriate, an overnight hospital stay may be required following implantation.

VNS therapy provides adjunctive therapy to AEDs and should only be used for patients who are refractory to AED therapy, are unsuitable candidates for resective surgery, or for whom surgery is not an option.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health-financing decisions in Australia. The MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision-making when funding is sought under Medicare. A team from Adelaide Health Technology Assessment, Discipline of Public Health, School of Population Health and Clinical Practice, The University of Adelaide, was engaged to conduct a systematic review of literature on vagus nerve stimulation for epilepsy. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of vagus nerve stimulation for epilepsy

Clinical need

Specific data regarding the prevalence of medically refractory epilepsy in Australia are not available. The point prevalence of epilepsy in Australia has been reported as 340 per 100,000 persons, of which one-third would be refractory to AED therapy. The number of hospital separations attributed to epilepsy in 2004–05 was 16,590, of which 5.4% were due to intractable epilepsy. This figure is likely to underestimate the number of people in Australia with medically refractory epilepsy as not all cases would be captured by data on hospital separations.

Expert opinion has suggested that 1% of the epilepsy population would be suitable for resective surgery. Further to this, it is suggested that approximately 30 patients would receive VNS annually, with eight of these being children.

Safety

The safety of VNS plus AED therapy was assessed in 39 studies and 25 case reports. No comparative data were available for evaluating VNS-related associated complications in children, and limited comparative data were available for adults. Complications associated with VNS therapy could be attributed to either the implantation procedure or the VNS device.

Death was reported in two patients (one adult and one child). The adult committed suicide after a worsening of psychiatric symptoms, while the child aspirated following a nocturnal seizure. In neither case was VNS clearly implicated in the deaths.

Other reported complications included pain (5–33%), infection (2–20%), dysphagia (2–13%), paraesthesia (2–19%), hoarseness (12–100%), coughing (1–46%), dyspnoea (2–25%) and device removal (2–38%). The most commonly reported adverse event was hoarseness and coughing, of which most cases were mild, transient or responsive to a reduction of stimulation parameters.

The majority of complications associated with VNS or the implantation of the device are likely to be considered acceptable by people with epilepsy. However, VNS therapy is provided as an adjunct to AED therapy and, as such, the adverse events of VNS therapy occur in addition to those of AED therapy. Therefore, it must be concluded that VNS plus AED therapy is not as safe as AED therapy alone.

Effectiveness

The effectiveness of VNS plus AED therapy was assessed with data supplied from 49 studies for a number of outcomes. Level II intervention evidence was provided in one study and level III-2 intervention evidence in three other studies.

Comparative evidence was unavailable regarding the effect of VNS plus AED therapy relative to AED therapy alone on epilepsy-related mortality. However, VNS is unlikely to have increased the rate of deaths in excess of those occurring due to epilepsy-related causes.

The effectiveness of VNS plus AED therapy in improving patient quality of life is difficult to determine as it is unlikely that the instruments used to assess this outcome were sufficiently sensitive to detect a change in the population of patients studied. It is the expert opinion of the Advisory Panel that quality of life improvements are seen in these patients following VNS therapy, and that the best indicator of such changes is a decrease in seizure frequency.

Statistically significant reductions in seizure frequency relative to AED therapy alone (6–8%) were seen in patients following VNS plus AED therapy (41–50%). A reduction of 50% in seizure frequency is considered to be clinically relevant; however, evidence suggests that such a reduction is likely to be seen in only 40% of patients.

The evidence regarding the effect of VNS plus AED therapy on drop attacks, a very debilitating seizure type, would suggest that a greater reduction is likely to be seen in children than adults. Marked and clinically important reductions in drop attacks were seen in children.

Continuation of VNS plus AED therapy was closely associated with a perceived clinical benefit to patients. Reported continuation rates in level IV intervention evidence was in the range 29–100%.

Economic considerations

A cost-effectiveness analysis was not performed due to a lack of adequate data and uncertainty surrounding the net benefit of VNS plus AED therapy (ie the trade-off between safety and effectiveness).

An analysis of the financial implications associated with providing VNS plus AED therapy indicates that the total healthcare costs would be an additional cost of $652,000 annually. This is based on the assumption that 30 patients would receive a VNS implant each year. Potential leakage could see this estimate significantly increased to $1,630,000 per year.

The greatest cost associated with VNS therapy is the cost of the device itself ($18,300). This cost would be borne by the patient (or their health insurer) unless performed in the public sector. It should be noted that this financial analysis does not consider the likely substantive downstream costs associated with battery depletion. This results in a new pulse generator being implanted, with associated surgical risks and costs (including the cost of a new pulse generator), approximately 1–16 years (depending on the level of stimulation required) after the previous implantation. These costs cannot be accurately estimated on the basis of the data available.

Because the uptake of this therapy per year is relatively small, the financial implications to the Australian healthcare system would not be considered a significant burden. Further, the expected uptake in the private sector is estimated to be four patients annually, and this would be associated with an annual initial cost to the Australian Government of $6,341 relative to AED therapy with or without the ketogenic diet.

Recommendation

The MSAC has considered the safety, effectiveness and cost-effectiveness for vagus nerve stimulation in addition to anti-epileptic medication for patients with medically refractory epilepsy. It was compared with continued or modified anti-epileptic drug therapy for all patients, and for children it was also compared with or without a ketogenic diet.

MSAC finds the procedure is reasonably safe in the context of the condition being treated.

MSAC finds there is insufficient evidence of effectiveness and net benefit of vagal nerve stimulation therapy for patients with medically refractory epilepsy.

Formal economic analysis was not conducted in view of the uncertainty of net clinical benefit.

MSAC recommends that public funding arrangements for vagus nerve stimulation for epilepsy remain unchanged.

The Minister for Health and Ageing noted this advice on 28 August, 2008.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of vagus nerve stimulation (VNS) for epilepsy. This is a therapeutic device for the management of epilepsy refractory to anti-epileptic drug (AED) therapy in patients for whom intracranial surgery is not suitable or has previously been unsuccessful. The MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. The MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The MSAC's terms of reference and membership are at Appendix A. The MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

The MSAC has considered the evidence for VNS therapy in addition to AED therapy for patients with medically refractory epilepsy and for whom resective surgery is either not an option or has previously failed to provide freedom from seizures.

Rationale for assessment

This assessment was undertaken as a consequence of an application from the Epilepsy Society of Australia (on behalf of the Australian and New Zealand Association of Neurologists and the Neurosurgical Society of Australasia) to have VNS for epilepsy (implantation, revision and/or removal of the pulse generator and/or lead) publicly funded on the Medicare Benefits Schedule.

In order to consider this application for public funding, the MSAC has commissioned an independent evaluator to assess the safety, effectiveness and cost-effectiveness of VNS for epilepsy.

Background

Epilepsy refers to a number of different syndromes characterised by recurrent seizures of various types and foci (Chang & Lowenstein 2003). It is a serious disorder which can occur in all age groups, and can be associated with co-morbidities including learning disabilities, neurological deficits and other medical conditions (Duncan et al 2006).

Seizures are caused by abnormal excessive or synchronous neuronal activity within the brain, and can be classified in a number of different ways including through their aetiology or clinical manifestation (Table 1) (Chandrasoma & Taylor 1991). Idiopathic epilepsies have no known cause, unlike symptomatic epilepsies which occur with a known or suspected abnormality within the central nervous system (Kohrman 2007). Classification can also be made according to the origin of the seizure (Table 2). Generalised epilepsies are characterised by seizures which begin simultaneously in both cerebral hemispheres. In partial (or focal) epilepsies, seizures originate in one or more localised foci and may then spread to other areas of the brain (Benbadis 2001; Chang & Lowenstein 2003). Partial seizures may be further classified as simple (no loss of consciousness) or complex (loss of consciousness) (Benbadis 2001).

Table 1 Common generalised seizure types

Seizure type	Clinical features	Postictal	Duration	Associated epilepsy syndromes
Absence	Abrupt onset of staring with cessation of motor activity	Abrupt return to normal	<30 seconds	Childhood absence epilepsy, juvenile absence epilepsy
Myoclonic	Brief contraction of muscle groups either singularly or repetitively	Abrupt return to normal	<5 seconds	Idiopathic generalised epilepsies, Lennox-Gastaut syndrome, progressive myoclonus epilepsis
Tonic-clonic	May begin with a cry or fall to the ground followed by tonic flexion. This is followed by a clonic phase involving symmetrical movement of all limbs. Autonomic features are common as are incontinence and tongue biting.	Drowsiness may be prolonged, with recovery taking minutes to hours. Postictal confusion and agitation are common.	Usually <5 minutes	May be generalised from onset or secondarily with focal onset. Associated with a broad range of epilepsies
Tonic	Tonic extension of all limbs with semi-flexed arms (bear hug). Patients often fall backwards.		10 seconds	Symptomatic generalised epilepsies, particularly Lennox-Gastaut syndrome
Atonic	Classic drop attacks with sudden loss of postural tone		Few seconds	Symptomatic generalised epilepsies, including Lennox-Gastaut syndrome

Table 2 Common partial seizure types

Location	Clinical features
Temporal	Aura may involve epigastric sensation, olfactory or gustatory hallucinations, autonomic features, dysmnestic changes such as déjà vu followed by loss of awareness and automatisms involving the mouth or upper limbs. Duration 30–300 seconds with a brief period of postictal confusion.
Frontal	May be hyperkinetic with motor automatisms or an asymmetric tonic seizure depending on the location in the frontal cortex; may be incontinent.
Occipital	Visual symptoms including hallucinations, field defects and flashing lights; may vomit.

When diagnosing epilepsy it is important to differentiate between seizures and other causes of neurological disturbance (Stokes et al 2004). Typically, epilepsy is characterised by interictal (between seizure) epileptic activity as demonstrated by electroencephalography (EEG) findings of spikes and sharp wave activity (interictal epileptiform discharge). This, along with patient history, clinical features of seizures and, possibly, neuroimaging (magnetic resonance imaging (MRI) or computed tomography (CT)), may enable a diagnosis of epilepsy and the associated syndrome (Duncan et al 2006).

A number of epilepsies manifest in childhood or adolescence, including childhood and juvenile absence epilepsies, juvenile myoclonic epilepsy, West syndrome and benign occipital epilepsies. Accurate diagnosis of the particular syndrome can provide valuable information regarding patient management and prognosis (Guerrini 2006; Korff & Nordli 2006).

Epilepsy is associated with a mild increased risk of injury as a result of seizures, which can include burns, traffic accidents, head injuries and fractures (Tomson et al 2004). Epilepsy is also often associated with an increased risk of premature death related to the causes of epilepsy, such as neoplasia, cerebrovascular disease and pneumonia (Hitiris et al 2007). The cause of sudden unexplained death in epilepsy (SUDEP) is not yet known; however, associated risk factors include recent seizure (particularly generalised tonic-clonic seizure), mental retardation and the use of anti-epileptic drugs (AEDs) in polytherapy (Tomson et al 2004). The incidence of SUDEP is higher in patients with chronic epilepsy compared to those of recent onset. SUDEP may occur at any age but is more likely in those patients aged between 20 and 40 years (Tomson et al 2004).

The aim of treatment is to control seizures and thereby reduce the risk of morbidity and premature mortality, and improve patient quality of life.

Studies have shown that the quality of life for people with epilepsy is worse than that of the general population and equivalent to, or worse than, people with other chronic conditions. However, when epilepsy is well controlled, quality of life improves and is comparable to that of the general population (Berto 2002).

When epilepsy is not well controlled, the impact on quality of life can include social stigma, self-imposed isolation resulting from adverse effects of therapy, or isolation as a consequence of loss of a driving licence. In addition, people with epilepsy may also be restricted in their employment opportunities due to the need to avoid jobs of high stress and anxiety (Berto 2002).

The procedure

Vagus nerve stimulation (VNS) was first used to treat epilepsy in humans in 1988 (Penry & Dean 1990). VNS is provided through the implantation of the NeuroCybernetic Prosthesis (NCP) system (Cyberonics Inc.). The NCP comprises a pulse generator, bipolar lead, programming wand with accompanying NCP software, tunnelling tool and hand-held magnet (Wheless et al 2001).

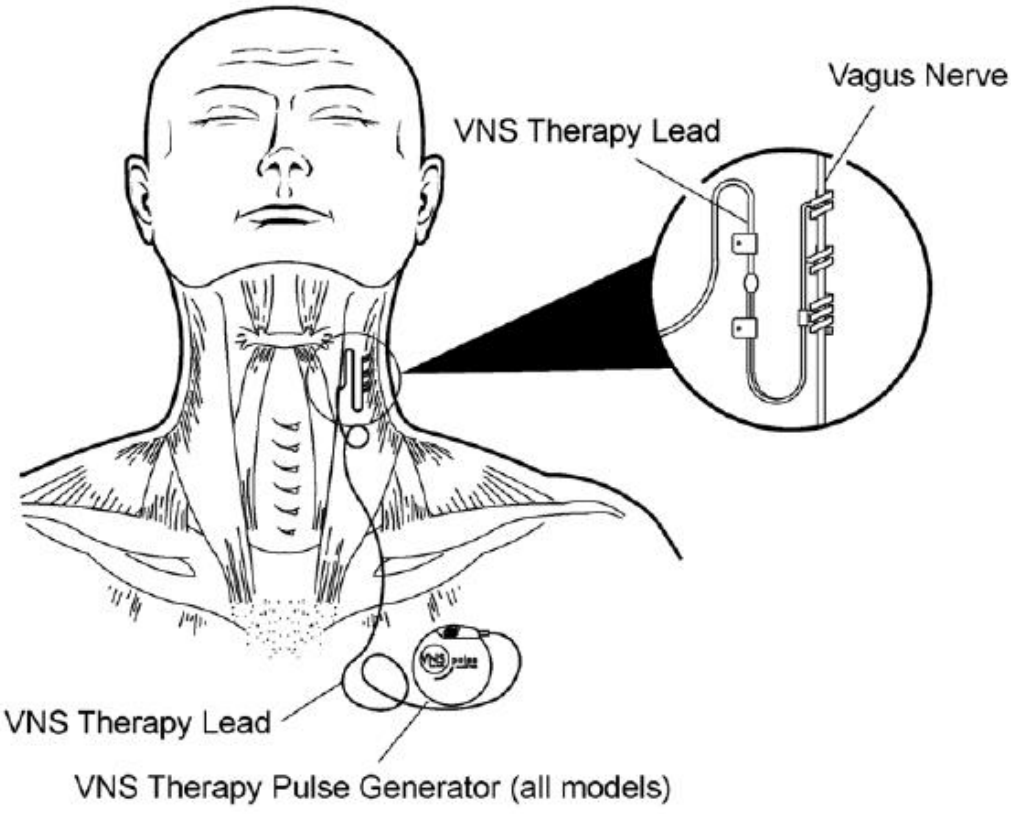


Figure 1 Implantation of VNS Therapy™ system

Implantation occurs under general anaesthesia and typically requires 1–2 hours to complete (Figure 1). The procedure is generally performed by a neurosurgeon but may also be performed by a head and neck or general surgeon. The bipolar lead is attached to the left vagus nerve in the neck through a small incision, and the pulse generator is placed in the upper chest through a separate incision. Once attached to the vagus nerve, the lead is tunnelled under the skin and connected to the pulse generator. The implantation procedure may involve an overnight stay to monitor the patient (Cyberonics Inc. 2006).

The NCP is programmed to provide regular electrical stimulation using the programming wand (Wheless et al 2001) (Figure 2). A hand-held magnet may also be used by patients or carers at the onset of a seizure to provide additional stimulation, or to cease stimulation when required, for example during public speaking (Cyberonics Inc. 2006). The manufacturers of this device warn that whole-body MRI should not be undertaken by patients with an implanted VNS device (Cyberonics Inc. 2006).

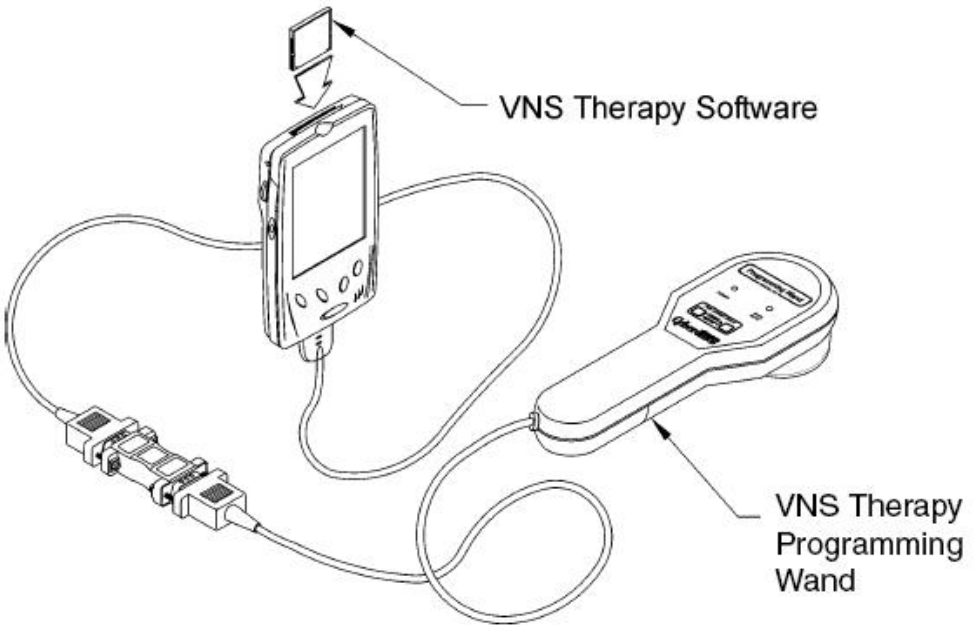


Figure 2 Programming of VNS Therapy™ system

The life of the battery in the pulse generator can vary between 1 and 16 years depending on the model and programmed settings. The pulse generator can be replaced after battery depletion in a simple outpatient procedure of 30–60 minutes' duration (Cyberonics Inc. 2006).

Intended purpose

VNS for epilepsy is indicated as adjunctive therapy for both adults and children with partial or generalised epilepsy which is refractory to AEDs and for whom intracranial surgery is either unsuitable or has been unsuccessful.

In particular, VNS may be used for patients with epilepsy who have:

- recurrent partial or generalised epileptic seizures
- seizures which impact adversely on their wellbeing, quality of life and/or safety
- seizures which have been refractory to adequate trials of AEDs including polytherapy and second generation AEDs
- not been successful with surgery, or who are not suitable for surgery
- seizures which, if reduced by 50% over a 2-year period, are likely to result in improved wellbeing, quality of life and safety.

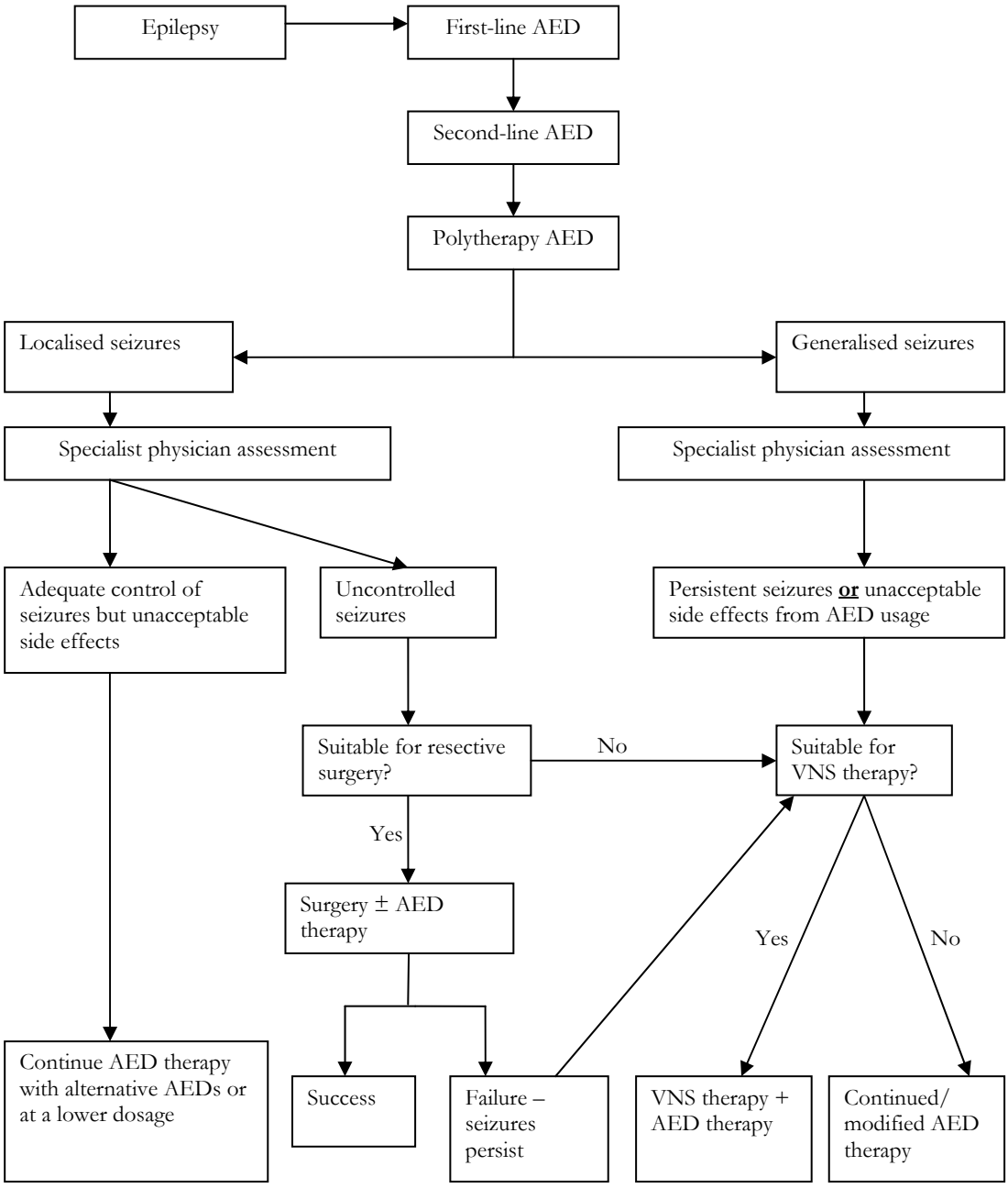
VNS for epilepsy is contraindicated for those patients in whom epilepsy:

- is adequately controlled with AED therapy without side effects
- is likely to be controlled without side effects after optimisation of AED therapy or epilepsy surgery
- has been treated previously with bilateral or left cervical vagotomy.

Existing procedures

The clinical decision-making process associated with the use of VNS for epilepsy in adults and children is presented in Figure 3 and Figure 4 respectively.

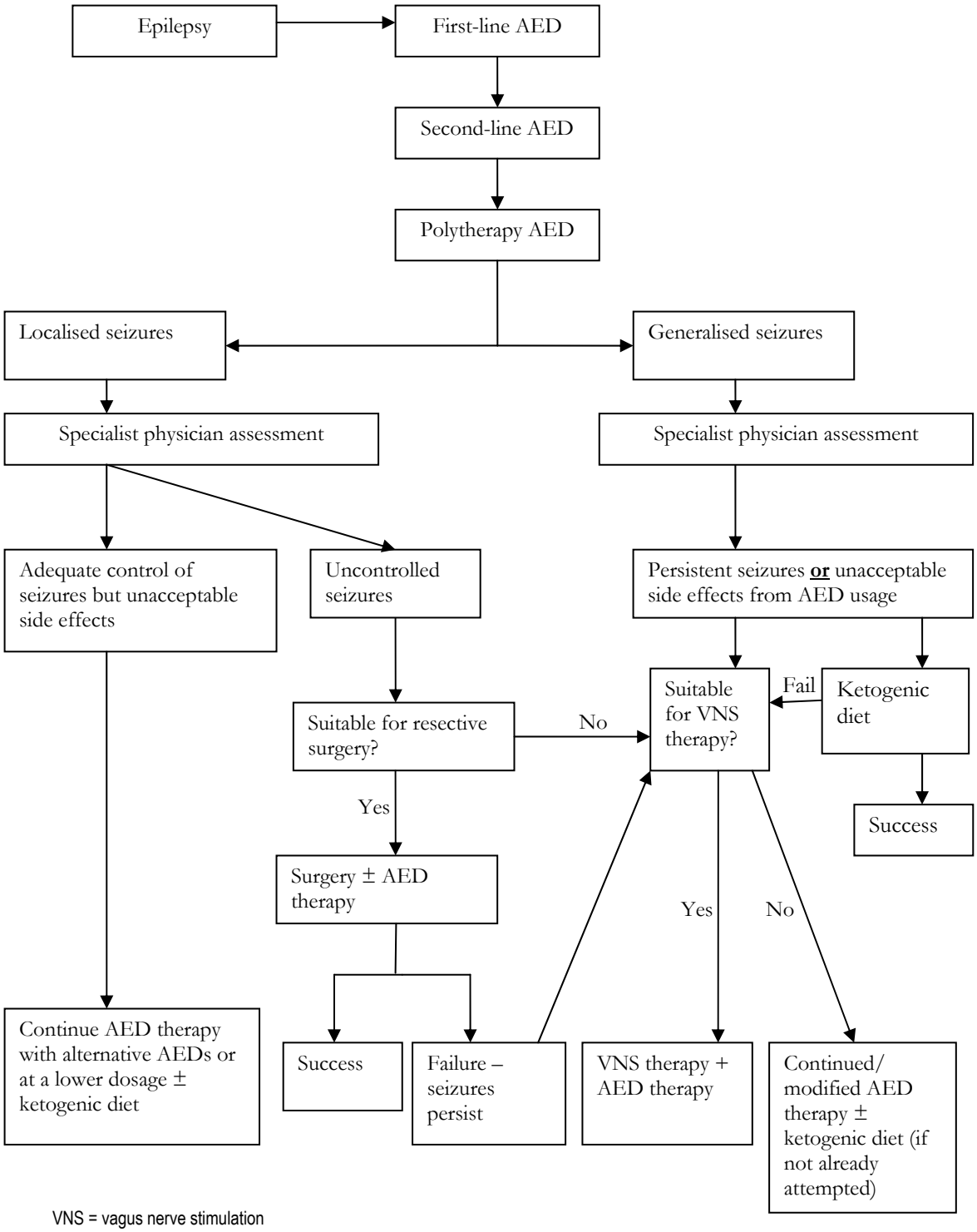
Figure 3 Clinical decision tree for management of epilepsy in adults



VNS = vagus nerve stimulation

AED = anti-epileptic drug

Figure 4 Clinical decision tree for management of epilepsy in children



VNS = vagus nerve stimulation

AED = anti-epileptic drug

Medication

AEDs aim to inhibit the aberrant firing of neurons. For the majority of patients with epilepsy, seizures can be controlled with the use of a single drug (Duncan et al 2006). For some patients, however, either persistent seizures or intolerable adverse effects from the drug will result in an alternative AED being trialled. If monotherapy fails, polytherapy should be attempted (Stokes et al 2004). Some evidence suggests that, if initial AEDs fail to control seizures, then the risk of subsequent AEDs proving ineffective is increased (Kwan & Brodie 2000). Kwan et al (2000) suggest that those patients who fail with the first drug due to lack of efficacy are more likely to fail with successive drugs than those who initially failed due to adverse reactions. It is estimated that approximately one-third of patients will be refractory to AEDs (Kwan & Brodie 2000). Side effects from AED therapy can be systemic, neurotoxic or idiosyncratic (Table 3). Intolerable side effects from medication are a major cause of poor compliance with treatment.

Intracranial surgery

Intracranial surgery may be an option for patients with partial seizures who continue to be refractory to AEDs. Resective surgery removes the portion of the brain from which the epileptic activity originates. Improvements in neuroimaging techniques have seen great improvement in patient outcomes following intracranial surgery (Foldvary et al 2001).

A rigorous evaluation is required prior to intracranial surgery to precisely define the eliptogenic region of the cortex. This includes a clinical history, ictal and interictal EEG, neuroimaging (eg MRI, single photon emission computed tomography (SPECT), positron emission tomography (PET) and CT). Patients will be recommended for intracranial surgery if there is a high likelihood of success (seizure freedom) and a low risk of neurologic and cognitive morbidity (Foldvary et al 2001).

Temporal lobe surgery is most commonly performed in adults, while extratemporal resection is most commonly performed in infants and during early childhood (Foldvary et al 2001). Seizure freedom as a consequence of temporal lobe resective surgery is achieved in 70% of patients, and 95% of patients achieve a 90% reduction in symptoms (Uijl et al 2005). Extratemporal resection is reported to achieve seizure freedom in 23–54% of patients, with an additional 25–35% reporting considerable improvement (Foldvary et al 2001).

Diet

The ketogenic diet was first used in the 1920s after observation that fasting provided relief from seizures (Wheless et al 2001). The diet is used in children, particularly those who suffer drop attacks. The aim is to maintain a state of ketosis by adherence to a diet high in fat and low in carbohydrates and protein (Wheless et al 2001). It is suggested that the use of ketones as an alternative fuel source for the brain may have an anti-convulsant effect (Hartman & Vining 2007).

The restrictiveness and unpalatability of the diet results in poor compliance. However, those who find it effective are more likely to be adherent (Wheless et al 2001). There are

also a number of adverse effects associated with the diet, including inadequate growth, dehydration, constipation, bruising, kidney stones, gastrointestinal complaints, cardiac complications and other metabolic effects (Hartman & Vining 2007).

Table 3 Side effects of some anti-epileptic medication

Drug	Systemic side effects	Neurotoxic side effects	Rare idiosyncratic reactions
First-line AED			
Carbamazepine	Nausea, vomiting, diarrhoea, hyponatraemia, rash, pruritus, fluid retention	Drowsiness, dizziness, blurred or double vision, lethargy, headache	Agranulocytosis, Stevens-Johnson syndrome, aplastic anaemia, hepatic failure, dermatitis, serum sickness, pancreatitis
Ethosuximide	Nausea, vomiting	Sleep disturbance, drowsiness, hyperactivity	Agranulocytosis, Stevens-Johnson syndrome, aplastic anaemia, dermatitis, serum sickness
Valproate	Weight gain, nausea, vomiting, hair loss, easy bruising	Tremor	Agranulocytosis, Stevens-Johnson syndrome, aplastic anaemia, hepatic failure, dermatitis, serum sickness, pancreatitis
Second-line AED			
Gabapentin	None known	Somnolence, dizziness, ataxia	Unknown
Lamotrigine	Rash, nausea	Dizziness, somnolence	Stevens-Johnson syndrome, hypersensitivity syndrome
Levetiracetam	Anorexia	Somnolence, dizziness, headache, nervousness	N/A
Phenytoin	Gingival hypertrophy, body hair increase, rash, lymphadenopathy	Confusion, slurred speech, double vision, ataxia, neuropathy (with long-term use)	Agranulocytosis, Stevens-Johnson syndrome, aplastic anaemia, hepatic failure, dermatitis, serum sickness
Phenobarbital	Nausea, rash	Alteration of sleep cycles, sedation, lethargy, behavioural changes	Agranulocytosis, Stevens-Johnson syndrome, hepatic failure, dermatitis, serum sickness
Pregabalin	Weight gain, peripheral oedema	Dizziness, somnolence, asthenia, headache, ataxia	N/A
Tiagabine	N/A	Dizziness, weakness, ataxia, nervousness, tremor, somnolence	N/A
Topiramate	Anorexia, weight loss	Confusion, cognitive slowing, dysphasia, dizziness, fatigue, paraesthesias	Nephrolithiasis, hypohidrosis, acute angle closure glaucoma

Reproduced with permission (Schachter 2007); AED = anti-epileptic drug; N/A = not applicable

Clinical need / burden of disease

The Australian Institute of Health and Welfare (AIHW) reports the point prevalence of epilepsy as occurring in 340 per 100,000 persons in 1996 (Australian Institute of Health and Welfare 2000). In addition, the Epilepsy Foundation of Victoria has estimated that

the lifetime prevalence of epilepsy occurs in 3,000 per 100,000 persons (Epilepsy Foundation of Victoria 2001).

Although mortality attributable to epilepsy is 1 per 100,000 deaths, there are considerable hospitalisations for which epilepsy is the principal diagnosis (Australian Institute of Health and Welfare 2000). In 2004–05 there were 16,590 hospital separations that were epilepsy-related, consisting of 49,486 patient days with an average length of stay of 3.0 days (Australian Institute of Health and Welfare 2007). Table 4 describes the hospital separations according to epilepsy syndrome and age.

Table 4 Hospital separations associated with epilepsy in 2004–05 stratified by age

Disease (ICD-10-AM code)	<5 years	5–14 years	15–34 years	35–59 years	>60 years
G40 Localisation-related (focal)(partial) idiopathic epilepsy and epileptic syndromes with seizures of localised onset	11	23	5	4	4
G40.1 Localisation-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures	96	104	130	174	167
G40.2 Localisation-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures	156	204	325	391	235
G40.3 Generalised idiopathic epilepsy and epileptic syndromes	436	596	1,304	1,386	691
G40.4 Other generalised epilepsy and epileptic syndromes	132	123	54	64	9
G40.5 Special epileptic syndromes	5	6	68	253	31
G40.6 Grand mal seizures, unspecified (with or without petit mal)	51	148	664	774	397
G40.7 Petit mal, unspecified, without grand mal seizures	8	12	32	35	36
G40.8 Other epilepsy	48	52	47	60	40
G40.9 Epilepsy, unspecified	486	736	1,928	2,621	1,231
Total	1,429	2,004	4,557	5,762	2,841

Source: (Australian Institute of Health and Welfare 2007)

Estimates suggest that up to 30% of the population with epilepsy are refractory to therapy (Kwan & Brodie 2000). While there are no data available to indicate the prevalence of intractable epilepsy within Australia, there are data which indicate the epilepsy-related hospitalisations, according to syndrome, with or without intractable epilepsy (Table 5). Hospital separations for intractable epilepsy contributed 5.4% of all hospitalisations from epilepsy in 2004–05. It should be noted that, while these data are indicative of hospitalisations due to severe epilepsy, they are unlikely to capture all people with intractable epilepsy. Health system costs attributable to epilepsy in 1993–94 were over $157 million (Australian Institute of Health and Welfare 2000, 2007).

Table 5 Hospital separations attributable to epilepsy or intractable epilepsy (2004–05)

Disease (ICD-10-AM code)	Hospital separations	Without mention of intractable epilepsy	With intractable epilepsy
G40 Localisation-related (focal)(partial) idiopathic epilepsy and epileptic syndromes with seizures of localised onset	47	40	7
G40.1 Localisation-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures	671	599	72
G40.2 Localisation-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures	1,311	1,161	150
G40.3 Generalised idiopathic epilepsy and epileptic syndromes	4,413	4,191	222
G40.4 Other generalised epilepsy and epileptic syndromes	379	254	125
G40.5 Special epileptic syndromes	363	352	11
G40.6 Grand mal seizures, unspecified (with or without petit mal)	2,034	1,942	92
G40.7 Petit mal, unspecified, without grand mal seizures	123	121	2
G40.8 Other epilepsy	247	213	34
G40.9 Epilepsy, unspecified	7,002	6,822	180
Total	16,590	15,695	895

Source: (Australian Institute of Health and Welfare 2007)

There is insufficient evidence to identify the likely number of procedures which will be performed per year. Expert opinion of the MSAC Advisory Panel (2008) estimates there will be approximately 30 VNS implantations per year.

Comparator

The proposed comparator to VNS for epilepsy is continued AED therapy with or without previous intracranial surgery. It is proposed that VNS would be used as adjunctive therapy in patients who are refractory to AEDs, and either unsuited or unsuccessful with intracranial surgery. Thus, intracranial surgery is not a comparator. Even though these patients are refractory to AED therapy, it is expected that they would still be receiving some form of AED therapy.

AED therapy uses either single agent or combination therapy (polytherapy) to reduce seizure frequency and consequently improve quality of life.

The Australian Medicines Handbook (AMH) (2007) recommends that a single first-line drug is used to begin treatment. Choice of AED is determined primarily by seizure type (Table 6) and initial doses are gradually titrated to maximise seizure control with tolerable side effects.

Table 6 Selection of AED

First-line AED	Second-line AED
Partial seizures	
Carbamazepine	Gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbitone, phenytoin, pregabalin[a], tiagabine, topiramate, valproate
Generalised tonic-clonic seizures	
Valproate, carbamazepine	Lamotrigine, oxcarbazepine, phenobarbitone, phenytoin, topiramate
Absence seizures	
Valproate, ethosuximide	Clobazam[a], clonazepam, lamotrigine
Myoclonic seizures	
Valproate	Clobazam[a], clonazepam, phenobarbitone
Infantile spasms	
Tetracosactrin (ACTH analogue), prednisolone	Clonazepam, nitrazepam, valproate, vigabatrin[b]

Reproduced with permission from Australian Medicines Handbook (2007)
[a] Not eligible for Pharmaceutical Benefits Scheme subsidy for this indication; [b] Use only if no safer alternative; AED = anti-epileptic drug; ACTH = adrenocorticotrophic hormone

If initial therapy is unsuccessful in preventing seizures or the side effects are unacceptable, it is recommended that an alternative first-line drug is added to the treatment regimen. When the optimal dosage is achieved, the dosage of the initial drug should be reduced gradually (Australian Medicines Handbook 2007).

Polytherapy is attempted after failure of single AEDs to obtain seizure control but is associated with an increased risk of toxic side effects (Duncan et al 2006). First-line drugs should be initially considered for polytherapy before the use of a second-line drug (Australian Medicines Handbook 2007).

If the patient remains seizure-free for 2–3 years, treatment withdrawal may be considered. Dosage of AEDs should be reduced gradually over a number of weeks to months (Australian Medicines Handbook 2007).

Marketing status

The VNS Therapy™ system is registered on the Australian Register of Therapeutic Goods under the following items:

ARTG number	Product description
112654	Model 102R - Stimulator, electrical, vagus nerve, antiseizure
131044	102 including 220 - Stimulator, electrical, vagus nerve, antiseizure
131045	102R including 220 - Stimulator, electrical, vagus nerve, antiseizure
131046	250 - Computer, palmtop
131047	302.20 and 302.30 - Electrode/lead, stimulator, implantable, neurological
130202	Tunneller, vascular
130203	Stimulator, electrical, vagus nerve, antiseizure

Current reimbursement arrangements

Currently, there is no listing on the Medicare Benefits Schedule (MBS) for the insertion, revision, reposition or removal of VNS Therapy™ system pulse generators or devices.

Specific AEDs are registered with the Therapeutic Goods Administration (TGA) and are subsidised through the Pharmaceutical Benefits Scheme (PBS). The cost of AED therapy is likely to vary between patients as drug regimens will be tailored to individual needs. The PBS-listed AEDs are given in Table 7.

Many of the drugs are available in different forms (ie capsule, tablet or oral suspension) and at different concentrations, and are produced by different manufacturers; consequently, only a single form has been described in Table 7. Pregabalin, a second-line AED used for partial seizures, is registered with the TGA but it is not eligible for PBS subsidy.

Table 7 PBS-listed AEDs

Listed AED [a]	Maximum quantity	Dispensed price for maximum quantity
First-line drug		
Carbamazepine	200 x 200 mg	$39.27
Clonazepam	200 x 2 mg	$38.48
Ethosuximide	200 x 250 mg	$52.94
Nitrazepam	50 x 5 mg	$10.19
Sodium valproate	200 x 200 mg	$32.22
Tetracosactrin	1 mg x 1 ml (injection)	$70.29
Second-line drug		
Gabapentin	100 x 300 mg	$79.56
Lamotrigine	56 x 200 mg	$142.23
Levetiracetam	60 x 250 mg	$62.57
Oxcarbazepine	100 x 150 mg	$71.29
Phenobarbitone	200 x 30 mg	$10.39
Phenytoin	200 x 50 mg	$28.11
Tiagabine hydrochloride	100 x 10 mg	$137.86
Topiramate	60 x 200 mg	$163.63
Vigabatrin	100 x 500 mg	$90.34

Source: (Department of Health and Ageing 2007b); PBS = Pharmaceutical Benefits Scheme; AED = anti-epileptic drug; [a] AED therapy (in terms of drugs used and doses required) will vary between individual patients.

Approach to assessment

Objective

To determine whether there is sufficient evidence in relation to clinical need, safety, effectiveness and cost-effectiveness, to have VNS therapy in addition to AED therapy in the treatment of refractory epilepsy listed on the MBS.

Research questions

1. Is VNS therapy adjunctive to AED therapy for the treatment of intractable epilepsy as safe as, or safer than, (i) continued AED therapy alone in adults or children, and (ii) AED therapy with ketogenic diet in children?

2. Is VNS therapy adjunctive to AED therapy for the treatment of intractable epilepsy as, or more, effective than (i) AED therapy alone in adults or children, and (ii) AED therapy with ketogenic diet in children?

3. Is VNS therapy adjunctive to AED therapy for the treatment of intractable epilepsy as, or more, cost-effective than (i) AED therapy alone in adults or children, and (ii) AED therapy with ketogenic diet in children?

Expert advice

An advisory panel with expertise in neurology, paediatric neurology, neurosurgery, consumer issues, general practice and general surgery was established to evaluate the evidence and provide advice to the MSAC from a clinical perspective. In selecting members for advisory panels, the MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the advisory panel is provided at Appendix B.

Review of literature

Literature sources and search strategies

VNS for refractory epilepsy was first mentioned in the literature in 1990; thus, the medical literature was searched to identify relevant studies and reviews for the period between 1990 and October 2007. Appendix C describes the electronic databases that were used for this search and the other sources of evidence that were investigated.

The search terms used to identify literature in electronic databases on the safety and effectiveness of VNS therapy for refractory epilepsy are also presented in Appendix C.

Selection criteria

The criteria for including articles in this report varied depending on the type of research question being addressed. Often a study was assessed more than once because it addressed more than one research question. One researcher applied the inclusion criteria to the collated literature. If there was any doubt concerning inclusion of papers, this was resolved by group consensus to ensure that all potentially relevant studies were captured. In general, studies were excluded if they:

- did not address the research question;
- did not provide information on the pre-specified target population;
- did not include the pre-specified intervention;
- did not compare results to the pre-specified comparators;
- did not address one of the pre-specified outcomes and/or provided inadequate data on these outcomes (in some instances, a study was included to assess one or more outcomes but had to be excluded for other outcomes due to data inadequacies); or
- did not have the study design specified in the review protocol.

Careful attention was given to studies in regard to the population studied. Inclusion criteria regarding the population were strictly adhered to. Studies were only included if they had indicated that patients were not eligible for resective surgery (including if neuroimaging, such as MRI, had indicated that there was no identifiable lesion) or had previously failed surgical treatment. Studies including patients who had been diagnosed with cryptogenic epilepsy were included, as were studies of patients with mixed seizures (ie partial and generalised seizures). **A clinical diagnosis of medically intractable epilepsy alone was not sufficient to be included in this review.**

Studies that did not explicitly indicate that patients were ineligible or had previously failed resective surgery, or did not provide sufficient information to deduce this from the paper, are given in the list of excluded studies at Appendix F.

The inclusion criteria relevant to each of the research questions posed in this assessment are provided in Box 1 to Box 4 in the results section of this report.

Search results

The process of study selection for this report went through six phases:

1. All reference citations from all literature sources were collated into an Endnote 8.0 database.
2. Duplicate references were removed.
3. Studies were excluded, on the basis of the citation information, if it was obvious that they did not meet the pre-specified inclusion criteria. Citations were assessed

independently by one reviewer. Studies marked as requiring further evaluation were retrieved for full-text assessment.

4. Studies were included to address the research questions if they met the pre-specified criteria, again independently applied by one reviewer to the full-text articles. Those articles meeting the criteria formed part of the evidence-base. The remainder provided background information.

5. The reference lists of the included articles were pearled for additional relevant studies. These were retrieved and assessed according to phase 4.

6. The evidence-base consisted of articles from phases 4 and 5 that met the inclusion criteria.

Any doubt concerning inclusions at Phase 4 was resolved by consensus between members of the evaluation team. The results of the process of study selection are provided in Figure 5

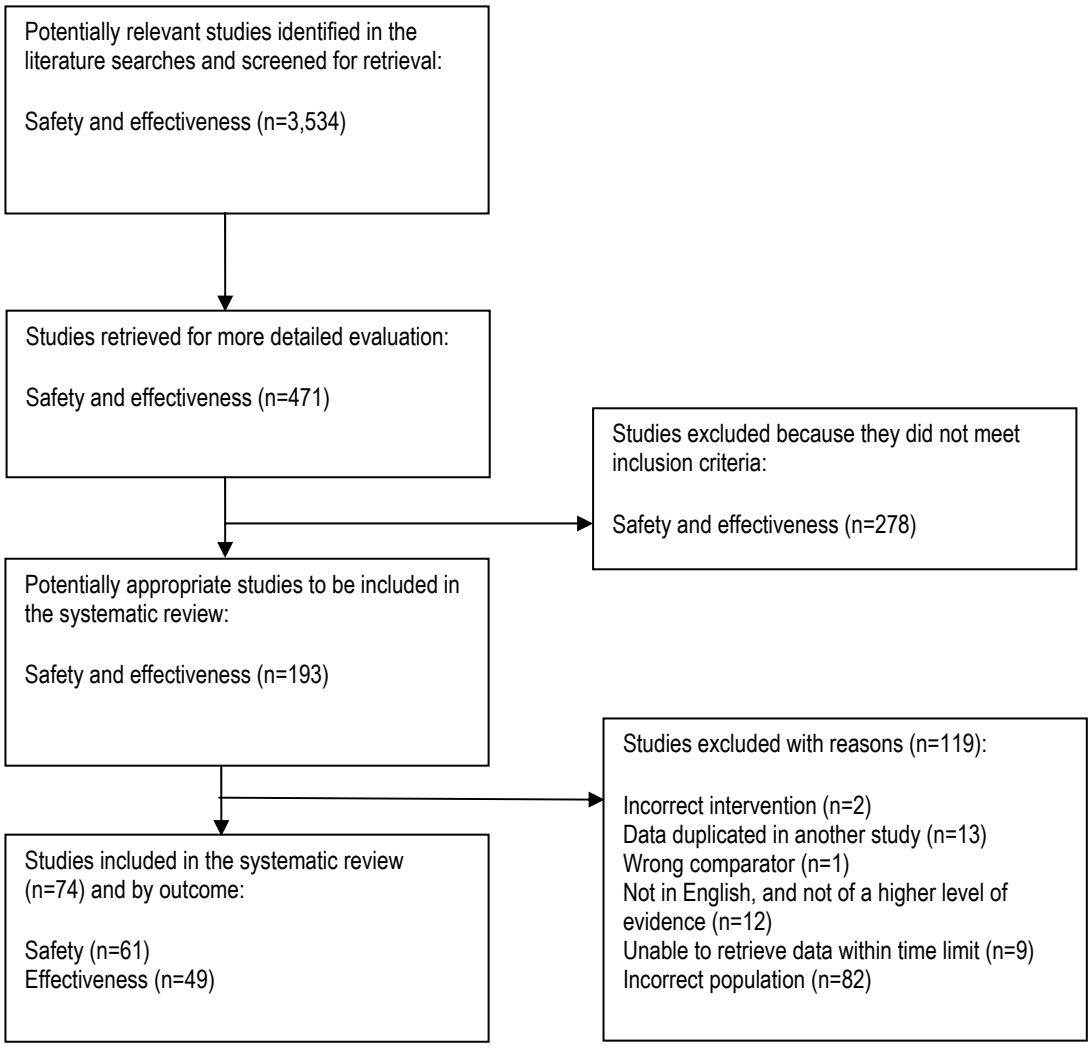


Figure 5 Results of study selection process

Data extraction and analysis

A profile of key characteristics including study design and location, level and quality of evidence, population, intervention and outcomes was developed for each study selected for this report (Appendix D).

Burden of disease has been reported as the prevalence of epilepsy within Australia.

Outcomes were assessed according to the age of the population studied (ie adults and children (≤18 years)). Where studies included both adults and children, the average age of the population studied was used to define the age category by which the study was assessed.

Descriptive statistics were extracted or calculated for all safety and effectiveness outcomes (defined in the assessment protocol) in the individual studies, including numerator and denominator information, means and standard deviations. Medians and inter-quartile ranges were reported for data that were not normally distributed. A statistically significant difference was assumed at $p<0.05$.

Assessment of effectiveness was largely concerned with determining whether there were reductions in seizure frequency from baseline. Differences between the intervention group and comparator at baseline have been considered to ensure that results reflect a real change due to the intervention rather than the result being affected by baseline differences between treatment groups. In instances where both baseline and follow-up data were provided for an outcome in intervention and comparator groups, the percentage difference between the pre- and post-intervention scores has been calculated within groups. In studies in which individual data has been reported, the overall mean of the change from baseline in individuals has been calculated; otherwise, the change in mean from baseline has been reported.

The majority of studies in this report were uncontrolled pre-test/post-test case series. Effectiveness data from both pre- and post-intervention have been presented, along with the percentage difference and the results of any statistical testing conducted by the authors.

Validity assessment of individual studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000b).

These dimensions (Table 8) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 8 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design[a]
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

[a] See Table 9.

Strength of the evidence

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence.

Level

The 'level of evidence' reflects the effectiveness of a study design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results.

The NHMRC evidence hierarchy provides a ranking of various study designs ('levels of evidence') by the type of research question being addressed (NHMRC 2008). Table 9 is an abbreviated version of this evidence hierarchy and includes the research question relevant to an assessment of an intervention.

Table 9 NHMRC evidence hierarchy: designations of 'levels of evidence' according to type of research question (including explanatory notes)

Level	Intervention[1]
I[2]	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudorandomised controlled trial (ie alternate allocation or some other method)
III-2	A comparative study with concurrent controls: – non-randomised, experimental trial[3] – cohort study – case-control study – interrupted time series with a control group
III-3	A comparative study without concurrent controls: – historical control study – two or more single arm studies[4] – interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Explanatory notes:
1 Definitions of these study designs are provided in NHMRC (2000b; pp 7–8).

2 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity, and thus are rated on the likelihood that the results have been affected by bias rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

3 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie using A vs B and B vs C to determine A vs C with statistical adjustment for B).

4 Comparing single arm studies, ie case series from two studies. This would also include unadjusted indirect comparisons (ie using A vs B and B vs C to determine A vs C but where there is no statistical adjustment for B).

5

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question, eg level II intervention evidence, level IV diagnostic evidence, level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: Bandolier editorial 1999; Lijmer et al 1999; NHMRC 1999; Phillips et al 2001.

Quality

The appraisal of intervention studies pertaining to treatment safety and effectiveness was undertaken using a checklist developed by the NHMRC (NHMRC 2000a). This checklist was used for trials and cohort studies. Uncontrolled before-and-after case series are a poorer level of evidence with which to assess effectiveness. The quality of this type of study design was assessed according to a checklist developed by the UK National Health Service (NHS) Centre for Reviews and Dissemination (Khan et al 2001).

Statistical precision

Statistical precision was determined using statistical principles. Small confidence intervals and p-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000b). Studies need to be assessed appropriately to ensure that a real difference between groups will be detected in the statistical analysis.

Size of effect

For intervention studies of VNS plus AED therapy, it was important to assess whether statistically significant differences between the comparators were also clinically important. The size of the effect needed to be determined, as well as whether the 95% confidence interval included only clinically important effects.

Relevance of evidence

The outcomes being measured in this report should be appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided (NHMRC 2000b). In this assessment of VNS plus AED therapy, the primary outcome of change in seizure frequency is considered clinically relevant. The secondary outcome concerning the number of patients who achieve a 50% reduction in seizure frequency would also be considered clinically important.

Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 2008). Five components are considered essential by the NHMRC when judging the body of evidence:

- the evidence-base—which includes the number of studies sorted by their methodological quality and relevance to patients;
- the consistency of the study results—whether the better quality studies had results of a similar magnitude and in the same direction, ie homogenous or heterogenous findings;
- the potential clinical impact—appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test;
- the generalisability of the evidence to the target population; and
- the applicability of the evidence—integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (Table 10) (NHMRC 2008).

Table 10 Body of evidence assessment matrix

Body of evidence / Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence-basea	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias, or a SR/multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population(s) studied in the body of evidence are the same as the target population	Population(s) studied in the body of evidence are similar to the target population	Population(s) studied in the body of evidence are different to target population for guideline but it is clinically sensible to apply this evidence to target population	Population(s) studied in the body of evidence are different to target population and it is hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Adapted from (NHMRC 2008)

Results of assessment

Is it safe?

Implantation and application of VNS therapy were assessed in terms of potential patient harms that may result from therapy in both the short and long terms. Studies addressing this issue were assessed for inclusion in this report according to the criteria defined, a priori, in Box 1 and Box 2. For the purposes of this assessment, the outcomes considered have been prioritised into primary and secondary safety outcomes, and the post-operative period has been considered as the 6 weeks following implantation or the period between implantation and activation.

Box 1 Inclusion criteria for identification of studies relevant to an assessment of safety of VNS therapy for intractable epilepsy in adults

Research question

Is VNS plus AED therapy as safe as, or safer than, AED therapy alone for adults with intractable epilepsy?

Selection criteria	Inclusion criteria
Population	Adults (>18 years) with localised epilepsy for whom seizures are uncontrolled, and who are not suitable for resective surgery or for whom surgery has been unsuccessful; also, adults with generalised epilepsy for whom seizures are uncontrolled or for whom side effects of AED therapy are unacceptable
Intervention	VNS therapy adjunctive to AED therapy
Comparator(s)	AED therapy with or without sham intervention
Outcomes	Primary outcomes:
	Adverse events including death, stroke, incisional pain, infection, dysphagia and paraesthesia (short and long term (>12 months))
	Secondary outcomes:
	Adverse events including voice alteration, cough, dyspnoea, fever, anorexia, emesis and abdominal pain (short and long term (>12 months))
Study design	Randomised or non-randomised controlled trials, cohort studies, registers, case series, case reports or systematic reviews of these study designs
Search period	1990 – 10/2007
Language	Studies in languages other than English were only translated and included if they represented a higher level of evidence than that available in the English language evidence-base.

AED = anti-epileptic drug; VNS = vagus nerve stimulation

Box 2 Inclusion criteria for identification of studies relevant to an assessment of safety of VNS therapy for intractable epilepsy in children

Research question

Is VNS plus AED therapy as safe as, or safer than, AED therapy alone with or without the ketogenic diet for children with intractable epilepsy?

Selection criteria	Inclusion criteria
Population	Patients (>2 years and ≤18 years) with intractable epilepsy with previous unsuccessful surgery, or for whom surgery is not suitable
Intervention	VNS therapy adjunctive to AED intervention
Comparator(s)	AED therapy with or without sham intervention, or ketogenic diet
Outcomes	Primary outcomes:
	Adverse events including death, stroke, incisional pain, infection, dysphagia and paraesthesia (short and long term (>12 months))
	Secondary outcomes:
	Adverse events including voice alteration, cough, dyspnoea, fever, anorexia, emesis and abdominal pain (short and long term (>12 months))
Study design	Randomised or non-randomised controlled trials, cohort studies, registers, case series, case reports or systematic reviews of these study designs
Search period	1990 – 10/2007
Language	Studies in languages other than English were only translated and included if they represented a higher level of evidence than that available in the English language evidence-base.

AED = anti-epileptic drug; VNS = vagus nerve stimulation

There were 39 studies and 25 case reports which reported on adverse events associated with the implantation of the VNS device and subsequent VNS therapy. The study profiles for all included studies and case reports are shown in Appendix D.

Data from the included studies have been entered into tables in a hierarchical manner according to each study's level of evidence, quality assessment, type of epilepsy and, then, alphabetically and most recently published. Tables depict results according to the population assessed—either that of adults or children. For studies which have assessed both adults and children, the average age of the population has been used to determine in which table the study was included.

Of the four comparative studies which were included in this report, only one study reported any adverse events following either VNS therapy or continuing AED therapy (Marrosu et al 2003). The primary aim of this study (level III-2 intervention evidence) was not to report on safety outcomes. However, it did report two events in order to explain the reduction in stimulation parameters in patients receiving VNS therapy. No other adverse events were reported as a consequence of either intervention. Therefore, only minimal, and possibly incomplete, comparative data are available for VNS plus AED therapy and AED therapy. No comparative safety data are available for VNS plus AED therapy relative to the use of ketogenic diet in children.

It should be noted that a substantial number of patients who received VNS therapy had some degree of mental retardation, with some subjects being severely mentally retarded and with limited communication abilities. Due to the reliance on reporting of adverse events by caregivers, the degree to which adverse events were accurately reported may have varied between this subpopulation and those without mental retardation or mental retardation to a lesser degree. This is likely to be of more consequence for outcomes such as pain and paraesthesia.

Primary safety outcomes

Peri-operative death

Death associated with VNS therapy was reported in two studies at rates between 1% and 6% (Casazza et al 2006; Smyth et al 2003).

In the study by Casazza et al (2006) (level IV intervention evidence), behavioural disturbance and psychiatric symptoms in a patient were subsequently followed by the patient committing suicide.

Smyth et al (2003) reported death due to aspiration following a seizure in a paediatric patient. Due to the uncontrolled nature of the study, it is unclear whether aspiration was due to VNS or as a result of an increased risk of aspiration in paediatric populations, particularly those with comorbid neurological disorders.

Table 11 Death associated with VNS therapy in adults

Study	Study design and quality appraisal	Population	Follow-up period	Frequency of death
Partial and generalised epilepsies				
(Casazza et al 2006)	Level IV case series Quality assessment: Fair	17 adult patients with medically retractable epilepsy who had previously failed resective surgery or were not suitable candidates	No adverse events	Suicide after VNS exacerbated behavioural and psychiatric symptoms = 1/17 (6%)

VNS = vagus nerve stimulation

Table 12 Death associated with VNS therapy in children

Study	Study design and quality appraisal	Population	Follow-up period	Frequency of death
Partial and generalised epilepsies				
(Smyth et al 2003)	Level IV retrospective case series Quality assessment: Good	74 consecutive paediatric patients with medically refractory multifocal or generalised epilepsy	Minimum = 12 months Mean = 2.2 years	Death due to aspiration secondary to tonic-clonic seizure = 1/74 (1%)

VNS = vagus nerve stimulation

Stroke

No studies which met the inclusion criteria for this review reported stroke as a consequence of implantation of the VNS system or associated with VNS therapy.

Pain

Pain resulting from implantation of the VNS device or from stimulation during VNS therapy was reported in 10 of the 39 studies reporting adverse events (Table 13 and

Table 14). The severity of pain varied greatly from mild to severe, with the latter prompting cessation of VNS therapy and removal of the VNS device. The site of pain varied from throat, incisional site, and neck and left ear, with the cause also varying. No comparative studies including VNS therapy were identified that reported pain as an outcome.

In adult populations pain was reported in 5–33% of patients. Studies which considered patients with partial epilepsies only reported pain in 20–23% of patients. In patients with generalised epilepsies only, pain was reported in 13–33% of patients.

Pain was reported as an outcome associated with VNS therapy in 5 of 18 studies in children. In these studies pain was described in 6–23% of patients (Table 14). In partial and generalised epilepsies pain was reported in 11% and 18–23% of children, respectively.

Pain in children varied from transient throat pain during stimulation to major pain requiring device removal. Pain was reported at the implantation site, throat and neck. Four of 50 (8%) patients reported non-specific pain associated with VNS therapy (Frost et al 2001).

Incisional/device pain

Pain as a result of implantation or from the device was not commonly reported. One good-quality low-level study (level IV intervention evidence) in adults reported incisional pain post-operatively or during follow-up in 13% of patients (Labar et al 1999).

In children incisional or device pain was reported by two studies (level IV intervention evidence) in 6–10% of patients (Frost et al 2001; Rychlicki et al 2006).

Stimulation pain

Pain as a consequence of stimulation occurred in 3–33% of patients in at least 6 of 10 studies which reported this adverse event. Pain was mostly transient and well tolerated; however, if required, it was relieved by the adjustment of stimulation parameters in most cases.

Stimulation pain occurred in adults and children at similar rates of 5–33% and 3–23%, respectively.

The fair-quality low-level study by Hosain et al (2000) (level IV intervention evidence) reported the highest incidence of pain (23%) associated with VNS therapy in a population of patients with Lennox-Gastaut syndrome. This study was limited by its small size but, additionally, by the inability of all patients to verbally report adverse events. Therefore, for those outcomes which can only be verbally expressed (eg pain and paraesthesia), the reported incidence may be underestimated.

Table 13 Pain associated with implantation or stimulation of the VNS system in adults

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Partial epilepsies			
(Alsaadi et al 2001)	Level IV case series Quality assessment: Good	10 adult patients with bilateral independent temporal lobe epilepsy. Patients were medically refractory and had failed intracranial surgery or were not considered suitable candidates	Throat discomfort during stimulation = 1/10 (10%)
(Fai et al 2004)	Level IV case series Quality assessment: Good	13 Chinese patients with medically refractory partial-onset seizures Mean age = 25 years (range 13–40)	Neck discomfort = 3/13 (23%)
(Marrosu et al 2003)	Level IV case series Quality assessment: Good	17 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery *VNS group*: (n=10) *Comparator – AED therapy:* (n=7) (adverse events occurring in comparator group were not reported)	*VNS group:* Throat pain during stimulation = 2/10 (20%)
(Ardesch et al 2007b)	Level IV case series Quality assessment: Fair	19 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Pain = 16%[a]
Generalised epilepsies			
(Holmes et al 2004)	Level IV case series Quality assessment: Good	16 patients with IGE or SGE aged 12 years or older	Throat pain during stimulation = 3/16 (19%)
(Labar et al 1999)	Level IV case series Quality assessment: Good	24 patients with generalised epilepsy which was medically refractory	Post-operative incisional pain = 1/24 (4%) Incisional pain during follow-up = 2/24 (8%) Overall: 3/24 (13%)
(Kostov et al 2007)	Level IV case series Quality assessment: Fair	12 patients with medically refractive idiopathic generalised epilepsy Mean age±SD = 31±14 years (range 11–48)	Throat pain = 3/12 (25%) Pain in ear = 1/12 (8%) Overall: 4/12 (33%)
Partial and generalised epilepsies			
(McLachlan et al 2003)	Level IV case series Quality assessment: Good	27 consecutive patients with medically refractory epilepsy (localised or generalised) who had failed resective surgery or were unsuitable candidates for such surgery Mean age = 30 years (range 12–46)	Severe neck and throat pain during stimulation = 2/27 (7%) Pain associated with stimulation = 1/27 (4%)[b] Minor pain = 2/27 (7%) Overall: 5/27 (19%)

(Ben-Menachem et al 1999)	Level IV case series Quality assessment: Fair	64 patients with medically refractory epilepsy who had failed resective surgery or were not suitable candidates for resective surgery	Throat pain = 3/64 (5%)
(Tanganelli et al 2002)	Level IV case series Quality assessment: Fair	47 patients with medically refractory epilepsy without indication for resective surgery	Pharyngodynia = 2/47 (4%) Diffuse pain requiring removal of VNS device = 1/47 (2%)[b] Overall: 3/47 (6%)

[a] Actual number of subjects reporting pain was not indicated; [b] see Table 31; AED = anti-epileptic drug; VNS = vagus nerve stimulation; N/A = not applicable; IGE = idiopathic generalised epilepsy; SGE = symptomatic generalised epilepsy

Table 14 Pain associated with implantation or stimulation of the VNS system in children

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Partial epilepsies			
(Rychlicki et al 2006) (Zamponi et al 2002)	Level IV case series Quality assessment: Good	36 children with refractory symptomatic or cryptogenic partial epilepsy	Sternocleidomastoid muscle spasm = 1/36 (3%) Major pain at implantation site = 2/36 (6%) Transient pharyngodynia = 1/36 (3%) Overall: 4/36 (11%)
Generalised epilepsies			
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	Transient pain at incisional site = 5/50 (10%) Non-specific pain = 4/50 (8%) Overall: 9/50 (18%)
(Hosain et al 2000)	Level IV case series Quality assessment: Fair	13 patients with Lennox-Gastaut syndrome Median age = 13 years (range 4–44)	Throat pain during stimulation (verbal patients) = 3/13 (23%)
Partial and generalised epilepsies			
(Hallbook et al 2005b)	Level IV case series Quality assessment: Fair	15 paediatric patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	Disabling pain in neck requiring stimulator withdrawal = 1/15 (7%)[a]
(Lundgren et al 1998a)	Level IV case series Quality assessment: Fair	16 children with intractable epilepsy who had failed intracranial surgery or were not suitable candidates	Transient throat pain requiring reduction in level of stimulation = 1/16 (6%)

[a] See Table 21 and Table 32; VNS = vagus nerve stimulation

Infection

Reports of infection ranged from superficial post-operative wound infection to delayed onset or persistent infections that required removal of the VNS device (Table 15 and Table 16). As such, the reporting of infection was, in part, dependent on the period of follow-up. Infection following implantation of the VNS device was reported in 13 of 39 studies included in the assessment of the safety of VNS therapy. Infection occurred at

rates of 2–20% and 3–11% of adult and child subjects, respectively, and often resulted in removal of the device.

Vonck et al (2004) reported two patients with delayed onset infection in a population of 118 patients (2%) in a fair-quality study (level IV intervention evidence). The infections occurred at 1 year, and 2 years and 9 months, follow-up respectively. One of the patients had fallen, resulting in a wound in the vicinity of the subclavicular incision site. The wound was poorly cleaned and subsequent infection developed. Surgical debridement of the surrounding tissue appeared to resolve the infection, but recurrence 7 months later resulted in removal of the generator and leads.

Wound infection was reported by Alexopoulos et al (2006) in 5 of 46 (7%) paediatric patients (level IV intervention evidence). These infections occurred between 1 week and 6 months following implantation of the VNS device. One patient was successfully treated with intravenous antibiotics, but the remaining four patients were required to have the VNS device explanted and only one patient had the device replaced.

Table 15 Infection following implantation of VNS system in adults

Study	Study design and quality appraisal	Population	Follow-up period	Peri-operative adverse events	Adverse events following implantation of VNS system	Total number of adverse events
Partial epilepsies						
(Alsaadi et al 2001)	Level IV case series Quality assessment: Good	10 adult patients with bilateral independent temporal lobe epilepsy. Patients were medically refractory and had failed intracranial surgery or were not considered suitable candidates	12 months	No adverse events	Infection resulting in device removal = 1/10 (10%)[a]	1/10 (10%)
Generalised epilepsies						
(Labar et al 1998)	Level IV case series Quality assessment: Fair	5 adults with medically refractive mixed symptomatic generalised epilepsy. All patients had been diagnosed with Lennox-Gastaut syndrome and one patient also had complex partial seizures.	9 months	Incisional infection requiring surgical debridement and IV[b] antibiotics = 1/5 (20%)	No adverse events	1/5 (20%)
Partial and generalised epilepsies						
(Boon et al 2001b) *Overlap of patients with Boon et al (2002)*	Level IV case series Quality assessment: Fair	35 patients with partial seizures or Lennox-Gastaut syndrome who were refractory to AEDs and unsuitable candidates for resective surgery	Mean±SD = 35 months (range 9–73)	Surgical wound infection = 1/35 (3%)	No adverse events	1/35 (3%)
(Tanganelli et al 2002)	Level IV case series Quality assessment: Fair	47 patients with medically refractory epilepsy without indication for resective surgery	Mean = 26 months (range 6–50)	No adverse events	Persistent local infection requiring device removal = 1/47 (2%)[a]	1/47 (2%)
(Vonck et al 2004) *Possible overlap with Boon et al (2001) and Boon et al (2002)*	Level IV case series Quality assessment: Fair	118 patients with medically refractory epilepsy who were not suitable candidates for resective surgery Mean age = 32 years (range 4–59)	Mean = 33 months (range 6–94)	No adverse events	Delayed-onset infection requiring device removal = 2/118 (2%)[a]	2/118 (2%)
(Andriola & Vitale 2001)	Level IV case series Quality assessment: Poor	21 patients with developmental disability or mental retardation. Patients had medically refractive epilepsy and were not suitable candidates for resective surgery Age range = 3–56 years	Range = 6 months – 3 years	Post-operative infection = 2/21 (10%)[a]	No adverse events	2/21 (10%)

[a] See Table 31; [b] IV = intravenous; VNS = vagus nerve stimulation; AED = anti-epileptic drug

Table 16 Infection following implantation of VNS generator in children

Study	Study design and quality appraisal	Population	Follow-up period	Peri-operative adverse events	Adverse events following implantation of VNS system	Total number of adverse events
Generalised epilepsies						
(Parker et al 1999)	Level IV case series Quality assessment: Good	16 consecutive children with cryptogenic epileptic encephalopathy refractory to AED therapy Mean age = 11±3 years	6, 12 and 24 months	Infection requiring device removal = 1/16 (6%)[a]	No adverse events	1/16 (6%)
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	Range = 1–6 months	Superficial wound infections = 2/50 (4%)	No adverse events	2/50 (4%)
(Hosain et al 2000)	Level IV case series Quality assessment: Fair	13 patients with Lennox-Gastaut syndrome Median age = 13 years (range 4–44)	6 months	No adverse events	Incisional infection requiring surgical debridement and antibiotics = 1/13 (8%)	1/13 (8%)
Partial and generalised epilepsies						
(Smyth et al 2003)	Level IV retrospective case series Quality assessment: Good	74 consecutive paediatric patients with medically refractory multifocal or generalised epilepsy	Minimum = 12 months Mean = 2.2 years	Deep infection requiring device removal = 3/74 (4%)[a] Superficial infection of stimulator site = 3/74 (4%)[a]	No adverse events	6/74 (8%)
(Patwardhan et al 2000)	Level IV case series Quality assessment: Fair	38 consecutive paediatric patients with medically refractive epilepsy *Note: Some of these patients were younger than 2 years old*	Median = 12 months (range 10–18)	No adverse events	Infection requiring device removal = 1/38 (3%)[a]	1/38 (3%)
(Saneto et al 2006) *Some subjects are also included in study by Arthur et al (2007)*	Level IV case series Quality assessment: Fair	63 children aged less than 12 years implanted with VNS	6–18 months	Infection requiring device removal = 2/63 (3%)[a]	No adverse events	2/63 (3%)

(Alexopoulos et al 2006)	Level IV case series Quality assessment: Poor	46 paediatric patients with medically refractory epilepsy who had failed previous resective surgery or were not suitable candidates for such surgery ≤ 12 years: n=21 > 12 years: n=25	Median = 2 years	Wound infection = 5/46 (11%)[a]	No adverse events	5/46 (11%)

[a] See Table 32; VNS = vagus nerve stimulation; AED = anti-epileptic drug

Dysphagia

Dysphagia is a difficulty in swallowing which can lead to aspiration of food or liquids into the lungs. This assessment identified 9 of 39 studies (level IV intervention evidence) with safety data which reported events of dysphagia. The incidence of dysphagia occurred in 2–13% of both adults and children (Table 17 and Table 18).

Although the incidence of dysphagia was limited and often resolved by decreasing stimulation settings, three children reported that dysphagia resulted in the necessity to deactivate VNS therapy during meals (Lundgren et al 1998a; Majoie et al 2005). In a small study (Table 19) of 16 paediatric patients by Lundgren et al (1998a) (level IV intervention evidence), two patients required inactivation of stimulation during mealtimes following incidents of aspiration. In addition to dysphagia, the two patients reported in the fair-quality low-level study by Lundgren et al (1998b) (level IV intervention evidence) showed proportional increases in aspiration during stimulation by the device when examined by video radiography during barium swallow (Lundgren et al 1998b).

Table 17 Dysphagia associated with VNS therapy in adults

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Partial epilepsies			
(Ardesch et al 2007b)	Level IV case series Quality assessment: Fair	19 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Occasional choking sensation during stimulation = 1/19 (5%)
Generalised epilepsies			
(Labar et al 1999)	Level IV case series Quality assessment: Good	24 patients with generalised epilepsy which was medically refractory	Dysphagia = 1/24 (4%)
Partial and generalised epilepsies			
(McLachlan et al 2003)	Level IV case series Quality assessment: Good	27 consecutive patients with medically refractory epilepsy (localised or generalised) who had failed resective surgery or were unsuitable candidates for such surgery Mean age = 30 years (range 12–46)	Dysphagia during stimulation = 2/27 (7%)
(Vonck et al 2004) *Possible overlap with Boon et al (2001) and Boon et al (2002)*	Level IV case series Quality assessment: Fair	118 patients with medically refractory epilepsy who were not suitable candidates for resective surgery Mean age = 32 years (range 4–59)	Gagging = 2/118 (2%)

VNS = vagus nerve stimulation

Table 18 Dysphagia associated with VNS therapy in children

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Generalised epilepsies			
(Majoie et al 2005)	Level IV case series Quality assessment: Good	19 children with childhood epilepsy resembling Lennox-Gastaut syndrome	Difficulty in swallowing resulting in device deactivation during meals = 1/19 (5%)
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	Dysphagia = 1/50 (2%)
Partial and generalised epilepsies			
(Smyth et al 2003)	Level IV retrospective case series Quality assessment: Good	74 consecutive paediatric patients with medically refractory multifocal or generalised epilepsy	Intermittent dysphagia = 2/74 (3%)
(Nagarajan et al 2002)	Level IV case series Quality assessment: Fair	16 children with medically refractive epilepsy who were unsuitable candidates for intracranial surgery	Transient choking episodes = 2/16 (13%)
(Patwardhan et al 2000)	Level IV case series Quality assessment: Fair	38 consecutive paediatric patients with medically refractive epilepsy *Note: Some of these patients were younger than 2 years old*	Transient, mild dysphagia = 3/38 (8%)

VNS = vagus nerve stimulation

Table 19 Aspiration associated with VNS therapy in children

Study	Study design and quality appraisal	Population	Aspiration following VNS therapy
Partial and generalised epilepsies			
(Lundgren et al 1998a)	Level IV case series Quality assessment: Fair	16 children with intractable epilepsy who had failed intracranial surgery or were not suitable candidates	Aspiration requiring inactivation of stimulator during mealtimes = 2/16 (13%)

VNS = vagus nerve stimulation

Paraesthesia

Paraesthesia is a subjective tingling sensation which was reported in 9 of 39 studies (Table 20 and Table 21). Reported paraesthesia was often mild and dose dependent (in terms of level of stimulation), and often declined over time.

In adults the incidence of paraesthesia was in the range 2–100%. Uthman et al (1993) reported the results of two studies (E01 and E02) (level IV intervention evidence). These were small, good-quality studies conducted at three centres in adult patients with partial epilepsies. Paraesthesia at the stimulation site was reported in all 14 subjects (100%) at initiation of active therapy. The authors indicated that more severe paraesthesia was reported in patients with increased stimulation settings.

Tanganelli et al (2002) reported adverse events in 47 patients with medically refractory epilepsy in a fair-quality study (level IV intervention evidence). Three subjects (6%)

reported paraesthesia in the left side of the neck and face during stimulation periods. The degree of paraesthesia was reduced over time.

In children the incidence of reported paraesthesia was small, with 6–8% of subjects reporting this event. Paraesthesia was generally mild; however, one patient had non-transient paraesthesia and pain associated with VNS therapy which resulted in withdrawal of the stimulator after the completion of the study.

Table 20 Paraesthesia following VNS therapy in adults

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Partial epilepsies			
(Uthman et al 1993) (Penry & Dean 1990) (Uthman et al 1990)	Level IV case series Quality assessment: Good	15 patients with medically refractory partial seizures EO1 study (n=11) EO2 study (n=4)	Tingling during stimulation = 14/14 (100%)
(Ardesch et al 2007b)	Level IV case series Quality assessment: Fair	19 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Paraesthesia = 16%[a]
Generalised epilepsies			
(Labar et al 1999)	Level IV case series Quality assessment: Good	24 patients with generalised epilepsy which was medically refractory	Post-operative incisional paraesthesia = 1/24 (4%) Incisional paraesthesia during follow-up = 2/24 (8%) Overall: 3/24 (13%)
(Kostov et al 2007)	Level IV case series Quality assessment: Fair	12 patients with medically refractive idiopathic generalised epilepsy Mean age±SD = 31±14 years (range 11–48)	Paraesthesia = 1/12 (8%)
Partial and generalised epilepsies			
(Ben-Menachem et al 1999)	Level IV case series Quality assessment: Fair	64 patients with medically refractory epilepsy who had failed resective surgery or were not suitable candidates for resective surgery	Paraesthesia = 1/64 (2%)
(Tanganelli et al 2002)	Level IV case series Quality assessment: Fair	47 patients with medically refractory epilepsy without indication for resective surgery	Paraesthesia = 3/47 (6%)

[a] Actual number of subjects reporting paraesthesia was not indicated; VNS = vagus nerve stimulation

Table 21 Paraesthesia following VNS therapy in children

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Generalised epilepsies			
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	Paraesthesia = 4/50 (8%)
Partial and generalised epilepsies			
(Hallbook et al 2005b)	Level IV case series Quality assessment: Fair	15 paediatric patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	Paraesthesia requiring stimulator withdrawal = 1/15 (7%)[b]
(Nagarajan et al 2002)	Level IV case series Quality assessment: Fair	16 children with medically refractive epilepsy who were unsuitable candidates for intracranial surgery	Paraesthesia = 1/16 (6%)

[a] Actual number of subjects reporting paraesthesia was not indicated; [b] see Table 14 and Table 32; VNS = vagus nerve stimulation

Secondary safety outcomes

Voice alteration

Voice alteration or hoarseness was reported in 27 of 39 studies. The overall incidence of hoarseness ranged between 12% and 100% in adults, and 8% and 53% in children (Table 22 and Table 23).

Stimulation-induced hoarseness

Stimulation-related hoarseness was reported in at least 10 of 16 studies of adult patients receiving VNS plus AED therapy. The majority of hoarseness was well tolerated and only occurred during stimulation periods. Transient hoarseness often occurred soon after an increase in stimulation settings and resolved within days.

Hoarseness was reported by 84% of subjects in the fair-quality low-level study conducted by Ardesch et al (2007) (level IV intervention evidence). One patient reported turning off the VNS device for 6 months due to the intolerability of hoarseness and paraesthesia which occurred during stimulation.

Patwardhan et al (2000) (level IV intervention evidence) reported the greatest number of children who suffered hoarseness, with 20 of 38 (53%) subjects reporting this outcome. The authors indicated, however, that this symptom was transient and occurred only during stimulation.

Alexopoulos et al (2006) reported that 57% of the paediatric population studied in their poor-quality study (level IV intervention evidence) reported transient stimulation-related

symptoms of hoarseness, cough, throat pain and drooling. The exact numbers of patients suffering each of these symptoms was not able to be extracted from the article.

Post-operative hoarseness

Vocal cord paralysis following implantation occurred in 1–11% of adults. Paralysis was often attributed to vagus nerve manipulation during surgery, and generally resolved within months of surgery. Vocal cord paralysis was not reported in the studies of children.

Uthman et al (1990) (level IV intervention evidence) reported hoarseness in 1 patient of 15 (7%) implanted with VNS, occurring several days after implantation. It was determined that sutures, used to aid in manipulating the electrodes during implantation, had in fact been placed around the vagus nerve. Subsequent nerve swelling and dysfunction resulted in the device being explanted before stimulation was initiated. The hoarseness resolved after several months.

Although no studies of children reported post-operative hoarseness or vocal cord paralysis, one study reported a patient who had a decrease in vocal volume. In this fair-quality study of 16 patients by Nagarajan et al (2002) (level IV intervention evidence), the patient reported the change in volume following replacement of the device after battery depletion.

Table 22 Voice alteration or hoarseness associated with VNS therapy in adults

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Partial epilepsies			
(Alsaadi et al 2001)	Level IV case series Quality assessment: Good	10 adult patients with bilateral independent temporal lobe epilepsy. Patients were medically refractory and had failed intracranial surgery or were not considered suitable candidates	Hoarseness during stimulation = 2/10 (20%)
(Uthman et al 1993) (Penry & Dean 1990) (Uthman et al 1990)	Level IV case series Quality assessment: Good	15 patients with medically refractory partial seizures EO1 study (n=11) EO2 study (n=4)	Hoarseness and vocal cord paralysis after implantation = 1/15 (7%)[a] Hoarseness during stimulation = 14/14 (100%) Overall: 15/15 (100%)
(Ardesch et al 2007b)	Level IV case series Quality assessment: Fair	19 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Hoarseness = 16/19 (84%) Vocal cord paralysis = 2/19 (11%)
(Koutroumanidis et al 2003)	Level IV case series Quality assessment: Fair	16 patients with medically refractory complex partial epilepsy who had failed previous resective surgery Mean age ± SD = 36 ±11.5 years (range 12–39)	Hoarseness = most patients
(Morrow et al 2000)	Level IV case series Quality assessment: Fair	10 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 32 years (range 16–54)	Post-operative hoarseness = 1/10 (10%) Transient hoarseness due to stimulation = 5/10 (50%) Overall: 6/10 (60%)
Generalised epilepsies			
(Holmes et al 2004)	Level IV case series Quality assessment: Good	16 patients with generalised epilepsy, aged 12 years or older	Voice alteration or hoarseness = 14/16 (88%)
(Kostov et al 2007)	Level IV case series Quality assessment: Fair	12 patients with medically refractive idiopathic generalised epilepsy Mean age±SD = 31±14 years (range 11–48)	Hoarseness = 3/12 (25%)
(Labar et al 1998)	Level IV case series Quality assessment: Fair	5 adults with medically refractive mixed symptomatic generalised epilepsy. All patients had been diagnosed with Lennox-Gastaut syndrome and one patient also had complex partial seizures.	Voice alteration during stimulation requiring reduced stimulation = 1/5 (20%)
Partial and generalised epilepsies			
(McLachlan et al 2003)	Level IV case series Quality assessment: Good	27 consecutive patients with medically refractory epilepsy (localised or generalised) who had failed resective surgery or were unsuitable candidates for such surgery Mean age = 30 years (range 12–46)	Post-operative vocal cord paralysis = 3/27 (11%) Hoarseness = 18/27 (67%)
(Ben-Menachem et al 1999)	Level IV case series	64 patients with medically refractory epilepsy who had failed resective	Hoarseness = 11/64 (17%) Vocal cord paralysis after replacement

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
	Quality assessment: Fair	surgery or were not suitable candidates for resective surgery	of lead = 1/64 (2%)
(Boon et al 2001b) *Overlap of patients with Boon et al (2002)*	Level IV case series Quality assessment: Fair	35 patients with partial seizures or Lennox-Gastaut syndrome who were refractory to AEDs and unsuitable candidates for resective surgery	Hoarseness or voice alteration during stimulation = 7/35 (20%)
(Casazza et al 2006)	Level IV case series Quality assessment: Fair	17 adult patients with medically retractable epilepsy who had previously failed resective surgery or were not suitable candidates	Voice alteration during stimulation = 17/17 (100%) Unacceptable hoarseness = 1/17 (6%)[a] Overall: 17/17 (100%)
(Chayasirisobhon et al 2003)	Level IV case series Quality assessment: Fair	34 patients with medically refractory epilepsy who were unsuitable for resective surgery Mean age = 27.6 years (range 5–70)	Hoarseness due to left vocal cord paralysis = 3/34 (9%) Intermittent hoarseness = 17/35 (50%) Overall: 20/35 (57%)
(Tanganelli et al 2002)	Level IV case series Quality assessment: Fair	47 patients with medically refractory epilepsy without indication for resective surgery	Moderate vocal hoarseness during stimulation = 19/47 (40%)
(Vonck et al 2004) *Possible overlap with Boon et al (2001) and Boon et al (2002)*	Level IV case series Quality assessment: Fair	118 patients with medically refractory epilepsy who were not suitable candidates for resective surgery Mean age = 32 years (range 4–59)	Continuous postoperative hoarseness = 1/118 (1%) Hoarseness during stimulation = 13/118 (11%) Overall: 14/118 (12%)
(Andriola & Vitale 2001)	Level IV case series Quality assessment: Poor	21 patients with developmental disability or mental retardation. Patients had medically refractive epilepsy and were not suitable candidates for resective surgery Age range = 3–56 years	Hoarseness = most patients Unilateral vocal cord paralysis = 1/21 (5%)

[a] See Table 31; SD = standard deviation; AED = anti-epileptic drug; VNS = vagus nerve stimulation

Table 23 Voice alteration or hoarseness associated with VNS therapy in children

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Partial epilepsies			
(Rychlicki et al 2006) (Zamponi et al 2002)	Level IV case series Quality assessment: Good	36 children with refractory symptomatic or cryptogenic partial epilepsy	Voice alteration associated with coughing, hoarseness and snoring following reimplantation of device due to lead fracture = 1/36 (3%)[a] Mild hoarseness during ramp-up = 14/36 (39%) Overall: 15/36 = 42%
Generalised epilepsies			
(Majoie et al 2005)	Level IV case series Quality assessment: Good	19 children with childhood epilepsy resembling Lennox-Gastaut syndrome	Hoarseness during stimulation which persisted until second month of stimulation = 7/19 (37%)
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	Hoarseness or voice alteration = 22/50 (44%)
(Hosain et al 2000)	Level IV case series Quality assessment: Fair	13 patients with Lennox-Gastaut syndrome Median age = 13 years (range 4–44)	Hoarseness = 3/13 (23%) (verbal patients)
Partial and generalised epilepsies			
(Hallbook et al 2005b)	Level IV case series Quality assessment: Fair	15 paediatric patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	Transient hoarseness after increasing stimulation = 4/15 (27%)
(Lundgren et al 1998a)	Level IV case series Quality assessment: Fair	16 children with intractable epilepsy who had failed intracranial surgery or were not suitable candidates	Transient hoarseness = 6/16(38%)
(Nagarajan et al 2002)	Level IV case series Quality assessment: Fair	16 children with medically refractive epilepsy who were unsuitable candidates for intracranial surgery	Hoarseness = 3/16 (19%) Change in auditory volume following reimplantation after battery depletion = 1/16 (6%) Overall: 4/16 (25%)
(Patwardhan et al 2000)	Level IV case series Quality assessment: Fair	38 consecutive paediatric patients with medically refractive epilepsy *Note: Some of these patients were younger than 2 years old*	Transient hoarseness during stimulation = 20/38 (53%)
(You et al 2007) (Kang et al 2006)	Level IV case series Quality assessment: Fair	28 paediatric patients with medically refractory epilepsy. All patients had either multifocal or generalised epilepsy and were therefore unsuitable candidates for resective surgery	Hoarseness = 7/28 (25%)
(Alexopoulos et al	Level IV case	46 paediatric patients with medically refractory epilepsy who had failed	Unable to extract data

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
2006)	series Quality assessment: Poor	previous resective surgery or were not suitable candidates ≤12 years: n=21 >12 years: n=25	
(Buoni et al 2004a)	Level IV case series Quality assessment: Poor	13 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 17 years (range 6–28)	Transient voice alteration = 1/13 (8%)

[a] See Table 32; VNS = vagus nerve stimulation

Cough

Coughing was reported in 21 of 39 studies included in this assessment of safety. The incidence of coughing in adult and child populations was similar, in the ranges 4–40% and 1–46% respectively (Table 24 and Table 25).

Most rates of coughing were transient and related to increased stimulation parameters. However, one patient in a fair-quality case series (level IV intervention evidence) required cessation of VNS therapy due to excessive and persistent coughing in spite of previous reductions in stimulation parameters (Labar et al 1998).

Table 24 Coughing associated with VNS therapy in adults

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Partial epilepsies			
(Fai et al 2004)	Level IV case series Quality assessment: Good	13 Chinese patients with medically refractory partial-onset seizures Mean age = 25 years (range 13–40)	Cough = 3/13 (23%)
(Uthman et al 1993) (Penry & Dean 1990) (Uthman et al 1990)	Level IV case series Quality assessment: Good	15 patients with medically refractory partial seizures EO1 study (n=11) EO2 study (n=4)	Cough = 1/15 (7%)
(Ardesch et al 2007b)	Level IV case series Quality assessment: Fair	19 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	During ramp-up, coughing during stimulation = 32%[a]
(Koutroumanidis et al 2003)	Level IV case series Quality assessment: Fair	16 patients with medically refractory complex partial epilepsy and who have failed previous resective surgery Mean age ± SD = 36±11.5 years (range 12–39)	Coughing = most patients
(Morrow et al 2000)	Level IV case series Quality assessment: Fair	10 patients with medically refractory epilepsy and who were unsuitable candidates for resective surgery Mean age = 32 years (range 16–54)	Transient coughing due to stimulation = 2/10 (20%)
Generalised epilepsies			
(Labar et al 1999)	Level IV case series Quality assessment: Good	24 patients with generalised epilepsy which was medically refractory	Coughing = 6/24 (25%)
(Kostov et al 2007)	Level IV case series Quality assessment: Fair	12 patients with medically refractive idiopathic generalised epilepsy Mean age±SD = 31 ±14 years (range 11–48)	Tickling in throat = 1/12 (8%)
(Labar et al 1998)	Level IV case series Quality assessment: Fair	5 adults with medically refractive mixed symptomatic generalised epilepsy. All patients had been diagnosed with Lennox-Gastaut syndrome and one patient also had complex partial seizures.	Coughing = 2/5 (40%) Spontaneous resolution = 1/2 Required cessation of VNS therapy despite reduced stimulation = 1/2
Partial and generalised epilepsies			
(McLachlan et al 2003)	Level IV case series Quality assessment: Good	27 consecutive patients with medically refractory epilepsy (localised or generalised) who had failed resective surgery or were unsuitable candidates for surgery Mean age = 30 years (range 12–46)	Cough = 6/27 (22%)
(Casazza et al 2006)	Level IV case series Quality assessment: Fair	17 adult patients with medically retractable epilepsy who had previously failed resective surgery or were not suitable candidates	Coughing when stimulation increased = 3/17 (18%)

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
(Tanganelli et al 2002)	Level IV case series Quality assessment: Fair	47 patients with medically refractory epilepsy without indication for resective surgery	Cough = 2/47 (4%)

[a] Actual number of patients reporting coughing was not indicated; VNS = vagus nerve stimulation

Table 25 Coughing associated with VNS therapy in children

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Partial epilepsies			
(Rychlicki et al 2006) (Zamponi et al 2002)	Level IV case series Quality assessment: Good	36 children with refractory symptomatic or cryptogenic partial epilepsy	Severe cough = 2/36 (5%)[a]
Generalised epilepsies			
(Holmes et al 2004)	Level IV case series Quality assessment: Good	16 patients with IGE or SGE aged 12 years or older	Mild coughing = 1/16 (6%)
(Majoie et al 2005)	Level IV case series Quality assessment: Good	19 children with childhood epilepsy resembling Lennox-Gastaut syndrome	Coughing which resolved after first week of stimulation = 4/19 (25%) Tickling in throat which resolved after first week of stimulation = 2/19 (11%)
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	Increased coughing when stimulation settings adjusted = 15/50 (30%)
(Hosain et al 2000)	Level IV case series Quality assessment: Fair	13 patients with Lennox-Gastaut syndrome Median age = 13 years (range 4–44)	Coughing when stimulator was on = 3/13 (23%) (verbal patients) Excessive coughing = 3/13 (23%) (reported by caregiver) Overall: 6/13 (46%)
Partial and generalised epilepsies			
(Smyth et al 2003)	Level IV retrospective case series Quality assessment: Good	74 consecutive paediatric patients with medically refractory multifocal or generalised epilepsy	Intermittent cough = 1/74 (1%)
(Hallbook et al 2005b)	Level IV case series Quality assessment: Fair	15 paediatric patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	Transient coughing after increasing stimulation = 4/15 (27%)
(Nagarajan et al 2002)	Level IV case series Quality assessment: Fair	16 children with medically refractive epilepsy who were unsuitable candidates for intracranial surgery	Transient coughing after increasing stimulation = most patients
(Patwardhan et al 2000)	Level IV case series Quality assessment: Fair	38 consecutive paediatric patients with medically refractive epilepsy *Note: Some of these patients were younger than 2 years old*	Transient cough during stimulation = 5/38 (13%)
(Buoni et al 2004a)	Level IV case series Quality	13 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Transient cough = 4/13 (31%)

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
	assessment: Poor	Mean age = 17 years (range 6–28)	

[a] See Table 31; IGE = idiopathic generalised epilepsy; SGE = symptomatic generalised epilepsy; VNS = vagus nerve stimulation

Dyspnoea

Dyspnoea or shortness of breath was reported in 13 of 39 studies which reported safety outcomes associated with VNS therapy. The range of incident dyspnoea was higher in adults (2–25%) than in children (2–7%) (Table 26 and Table 27). Most cases of dyspnoea were apparent during physical exertion and many resolved with a reduction in stimulation parameters.

Dyspnoea was reported in 16% of adult subjects with partial epilepsy in the fair-quality study by Ardesch et al (2006) (level IV intervention evidence). This included one subject who found it necessary to switch device stimulation off during exercise.

Koutroumanidis et al (2003) reported that most subjects, in a study of 16 adults with partial epilepsy (level IV intervention evidence), reported dyspnoea upon exertion, particularly at high levels of stimulation. This effect of VNS therapy was considered to be mild and reasonably well tolerated by patients.

Saneto et al (2006) (level IV intervention evidence) reported one child (2%) who had a worsening of respiratory symptoms following VNS implantation. This suggests that VNS therapy may have exacerbated pre-existing respiratory symptoms in the child. These symptoms resolved over time.

Table 26 Dyspnoea associated with VNS therapy in adults

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Partial epilepsies			
(Uthman et al 1993) (Penry & Dean 1990) (Uthman et al 1990)	Level IV case series Quality assessment: Good	15 patients with medically refractory partial seizures EO1 study (n=11) EO2 study (n=4)	Shortness of breath during exercise = 1/15 (7%)
(Ardesch et al 2007b)	Level IV case series Quality assessment: Fair	19 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Dyspnoea upon exertion = 16%[a]
(Koutroumanidis et al 2003)	Level IV case series Quality assessment: Fair	16 patients with medically refractory complex partial epilepsy who have failed previous resective surgery Mean age ± SD = 36±11.5 years (range 12–39)	Breathlessness upon exertion = most patients[a]
Generalised epilepsies			
(Labar et al 1999)	Level IV case series Quality assessment: Good	24 patients with generalised epilepsy which was medically refractory	Post-operative dyspnoea = 2/24 (8%)
(Kostov et al 2007)	Level IV case series Quality assessment: Fair	12 patients with medically refractive idiopathic generalised epilepsy Mean age±SD = 31±14 years (range 11–48)	Dyspnoea = 3/12 (25%)
Partial and generalised epilepsies			
(McLachlan et al 2003)	Level IV case series Quality assessment: Good	27 consecutive patients with medically refractory epilepsy (localised or generalised) who had failed resective surgery or were unsuitable candidates for such surgery Mean age = 30 years (range 12–46)	Shortness of breath = 5/27 (19%)
(Ben-Menachem et al 1999)	Level IV case series Quality assessment: Fair	64 patients with medically refractory epilepsy who had failed resective surgery or were not suitable candidates for resective surgery	Dyspnoea = 1/64 (2%)
(Boon et al 2001b) *Overlap of patients with Boon et al (2002)*	Level IV case series Quality assessment: Fair	35 patients with partial seizures or Lennox-Gastaut syndrome who were refractory to AEDs and unsuitable candidates for resective surgery	Dyspnoea upon exertion = 1/35 (3%)

[a] Actual number of subjects reporting dyspnoea was not indicated; SD = standard deviation; AEDs = anti-epileptic drugs; VNS = vagus nerve stimulation

Table 27 Dyspnoea associated with VNS therapy in children

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Partial epilepsies			
(Rychlicki et al 2006) (Zamponi et al 2002)	Level IV case series Quality assessment: Good	36 children with refractory symptomatic or cryptogenic partial epilepsy	Shortness of breath = 1/36 (3%)
Generalised epilepsies			
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	Dyspnoea upon exertion = 4%[a]
Partial and generalised epilepsies			
(Hallbook et al 2005b)	Level IV case series Quality assessment: Fair	15 paediatric patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	Shortness of breath = 1/15 (7%)
(Saneto et al 2006) *Some subjects are also included in study by Arthur et al (2007)*	Level IV case series Quality assessment: Fair	63 children aged less than 12 years, implanted with VNS	Worsening respiratory symptoms post-operatively = 1/63 (2%)
(You et al 2007) (Kang et al 2006)	Level IV case series Quality assessment: Fair	28 paediatric patients with medically refractory epilepsy. All patients had either multifocal or generalised epilepsy and were therefore unsuitable candidates for resective surgery	Dyspnoea during sleep = 2/28 (7%)

[a] Actual number of subjects reporting dyspnoea was not indicated; VNS = vagus nerve stimulation

Fever

Fever was reported in only 2 of the 39 included safety studies. One adult of 24 (4%) in a good-quality study (level IV intervention evidence) by Labar et al (1999) reported post-operative fever. The patient had an incisional infection which required treatment with antibiotics and surgical debridement before it resolved.

Smyth et al (2003) reported fever of unknown origin in one patient (1%) in a consecutive series of 74 patients (level IV intervention evidence). The work-up for the fever was complicated by an inactive VNS device, which was subsequently explanted.

Anorexia

Anorexia or weight loss was reported in four studies (Table 28). The incidence was 4% in adults and 4–25% in children receiving VNS therapy.

The good-quality study by Labar et al (1999) (level IV intervention evidence), whose subjects included some children, reported anorexia in 1 of 24 patients (4%).

The fair-quality study by Nagarajan et al (2002) (level IV intervention evidence) reported weight loss in 4 of 16 children (25%) in an Australian setting. The authors also indicated that one of the four subjects who reported weight loss required nutritional supplementation.

Table 28 Anorexia associated with VNS therapy in children

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Generalised epilepsies			
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	Anorexia = 2/50 (4%)
Partial and generalised epilepsies			
(Hallbook et al 2005b)	Level IV case series Quality assessment: Fair	15 paediatric patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	Weight loss = 1/15 (7%)
(Nagarajan et al 2002)	Level IV case series Quality assessment: Fair	16 children with medically refractive epilepsy who were unsuitable candidates for intracranial surgery	Weight loss = 4/16 (25%) Nutritional supplement required = 1/4

VNS = vagus nerve stimulation

Nausea or vomiting

Emesis (vomiting) or nausea was reported in 5 of 39 studies which met the criteria for inclusion in the safety assessment of VNS therapy (Table 29 and Table 30). Reports of emesis ranged, similarly, between 4% and 7% in adults and 2% and 6% in child populations studied.

In the good-quality study by Uthman et al (1993) (level IV intervention evidence), 1 adult subject among 15 (7%) reported nausea and vomiting near the end of battery life of the stimulator. In this instance the device reset to high stimulation settings on two occasions, leading to subsequent nausea and vomiting. The patient used the magnet to inactivate stimulation prior to the device being replaced. After replacement, the patient suffered no further symptoms. It is important to note that devices have since been modified to turn stimulation off instead of resetting to high stimulation parameters at the end of battery life.

Rychliki et al (2006) reported on adverse events in a good-quality series involving 36 children (level IV intervention evidence). Two children (6%) reported vomiting (associated with coughing) following electrode replacement. These symptoms were overcome by applying lower current output at longer intervals.

Table 29 Emesis associated with VNS therapy in adults

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Partial epilepsies			
(Uthman et al 1993) (Penry & Dean 1990) (Uthman et al 1990)	Level IV case series Quality assessment: Good	15 patients with medically refractory partial seizures EO1 study (n=11) EO2 study (n=4)	Nausea and vomiting near end of battery life = 1/15 (7%)
Generalised epilepsies			
(Labar et al 1999)	Level IV case series Quality assessment: Good	24 patients with generalised epilepsy which was medically refractory	Emesis = 1/24 (4%)
Partial and generalised epilepsies			
(McLachlan et al 2003)	Level IV case series Quality assessment: Good	27 consecutive patients with medically refractory epilepsy (localised or generalised) who had failed resective surgery or were unsuitable candidates for such surgery Mean age = 30 years (range 12–46)	Continuous vomiting which was responsive to reduction in stimulation = 1/27 (4%)

VNS = vagus nerve stimulation

Table 30 Emesis associated with VNS therapy in children

Study	Study design and quality appraisal	Population	Adverse events following implantation of VNS system
Partial epilepsies			
(Rychlicki et al 2006) (Zamponi et al 2002)	Level IV case series Quality assessment: Good	36 children with refractory symptomatic or cryptogenic partial epilepsy	Vomiting following electrode replacement = 2/36 (6%)[a] Nausea with increased stimulation = 1/36 (3%)
Generalised epilepsies			
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	Vomiting after stimulation began = 1/50 (2%)

[a] See Table 32; VNS = vagus nerve stimulation

Abdominal pain

Abdominal pain was described in only two studies which reported adverse events following VNS therapy. Within these studies, the incidence of abdominal pain was in the range 4–8%.

The good-quality study by Labar et al (1999) indicated 2 of 24 adults (8%) had reported mild abdominal pain following VNS therapy. The authors did not indicate if this symptom resolved over time or required a reduction in stimulation parameters.

Frost et al (2001), in describing adverse events in children (level IV intervention evidence), reported 2 of 50 children (4%) with stomach or intestinal upset. The severity or duration of this symptom also was not indicated.

Other adverse events

Other adverse events in addition to those described above were reported in 27 of the 39 studies (Table 31 and Table 32) (level IV intervention evidence).

Surgical revisions were reported in seven studies with frequencies in the range 2–25% of adult patients and 4–18% of children. The majority of revisions were the result of necessary device readjustments, including electrode replacement or reconnection, generator replacement or repositioning. Smyth et al (2003) described one child with delayed development and poor communication who was found to have a fractured lead. This was likely due to the child pulling at the neck and chest incisions following stimulation, causing subsequent rotation of the generator device.

In the fair-quality study reported by Tanganelli et al (2002), two patients had necrosis at the implantation site at 4 and 5 months following surgery. The authors proposed that this was a result of ischaemic damage to the tissue from compression of the skin by the generator device. The complication was resolved with surgical revision and deeper placement of the device. As a consequence of these two adverse events, all subsequent implantations were placed more deeply.

During the implantation procedure, testing is conducted to ensure optimum functioning of the VNS device and circuitry. Bradycardia during intraoperative testing occurred in two studies of adult populations (Ardesch et al 2007b; Vonck et al 2004). In the fair-quality study by Ardesch et al (2007), 2 of 19 (11%) subjects experienced intraoperative arrhythmia. Implantation proceeded and no further events occurred during follow-up. Vonck et al (2004) also reported arrhythmia during intraoperative testing in 1 patient of 118 (1%). Again, implantation proceeded and no further events were reported during follow-up.

In the study by Rychlicki et al (2006) (level IV intervention evidence), 6 of 36 (17%) children developed hypertrophic chest scars following implantation. These events all occurred at the beginning of the study and were followed by a change in operative technique, suggesting a learning curve involved with the implantation of the device.

Device removal

Removal of the VNS device was reported in 16 studies. The incidence of VNS device removal was in the range 2–38% and 3–9% in adults and children, respectively. In adults, removal was primarily due to lack of clinical efficacy, whereby there was no improvement in seizure frequency, or seizure frequency had worsened. Of 27 device removals in adults, 16 (59%) were performed for inadequate clinical efficacy. In contrast, only 2 of 14 (14%) device removals performed in children were undertaken due to a lack of clinical efficacy in reducing seizures. The primary reason for removal in children was due to infection, with 9 of 14 (64%) occurrences for this reason. In adults, infection was responsible for 6 of 27 (22%) of device removals.

Table 31 Other adverse events following implantation of VNS system in adults

Study	Study design and quality appraisal	Population	Peri-operative adverse events	Adverse events following implantation of VNS system
Partial epilepsies				
(Alsaadi et al 2001)	Level IV case series Quality assessment: Good	10 adult patients with bilateral independent temporal lobe epilepsy. Patients were medically refractory and had failed intracranial surgery or were not considered suitable candidates.	No adverse events	Device removal following infection = 1/10 (10%)[a]
(Fai et al 2004)	Level IV case series Quality assessment: Good	13 Chinese patients with medically refractory partial-onset seizures Mean age = 25 years (range 13–40)	No adverse events	Keloid scar over incisional wound = 1/13 (8%) Device removal due to lack of efficacy = 5/13 (38%)
(Uthman et al 1993) (Penry & Dean 1990) (Uthman et al 1990)	Level IV case series Quality assessment: Good	15 patients with medically refractory partial seizures EO1 study (n=11) EO2 study (n=4)	No adverse events	Complications due to lead wire fracture = 9/15 (60%) Device removal due to nerve swelling and dysfunction = 1/15 (7%)[b] Muscle movement in neck = 4/15 (27%) Uncontrolled hiccoughs = 1/15 (7%) Sleep disturbance when stimulation on = 1/15 (7%)
(Ardesch et al 2007b)	Level IV case series Quality assessment: Fair	19 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Intraoperative bradycardia during device testing = 2/19 (11%)	Device removal due to lack of efficacy = 2/19 (11%)
(Kawai et al 2002)	Level IV case series Quality assessment: Fair	15 patients with medically refractory partial epilepsy who had failed resective surgery or were not suitable	No adverse events	Device removal = 3/13 (23%) Lack of clinical efficacy = 2/3 Elected to undergo resective surgery = 1/3
(Koutroumanidis et al 2003)	Level IV case series Quality assessment: Fair	16 patients with medically refractory complex partial epilepsy who had failed previous resective surgery Mean age ± SD = 36±11.5 years (range 12–39)	No adverse events	Device removal due to severe worsening of epilepsy = 1/16 (6%)
Generalised epilepsies				
(Labar et al 1999)	Level IV case series Quality assessment: Good	24 patients with generalised epilepsy which was medically refractory	No adverse events	Surgical debridement of incisional infection = 1/24 (4%) Hiccoughs = 1/24 (4%) Fatigue = 1/24 (4%)
(Kostov et al 2007)	Level IV case series Quality	12 patients with medically refractive idiopathic generalised epilepsy	No adverse events	Tachycardia = 2/12 (17%) Insomnia = 1/12 (8%)

Study	Study design and quality appraisal	Population	Peri-operative adverse events	Adverse events following implantation of VNS system
	assessment: Fair	Mean age±SD = 31±14 years (range 11–48)		Surgical revision = 3/12 (25%) Lead problems = 2/3 Generator migration = 1/3
Partial and generalised epilepsies				
(McLachlan et al 2003)	Level IV case series Quality assessment: Good	27 consecutive patients with medically refractory epilepsy (localised or generalised) who had failed resective surgery or were unsuitable candidates for such surgery Mean age = 30 years (range 12–46)	No adverse events reported	Heartburn = 1/27 (4%) Device removal due to stimulation associated pain = 1/27 (4%)
(Ben-Menachem et al 1999)	Level IV case series Quality assessment: Fair	64 patients with medically refractory epilepsy who had failed resective surgery or were not suitable candidates for resective surgery	No adverse events	Complained of generator placement which was moved twice without improvement = 1/64 (2%)
(Casazza et al 2006)	Level IV case series Quality assessment: Fair	17 adult patients with medically refractory epilepsy who had previously failed resective surgery or who were not suitable candidates	No adverse events	Faecal and urinary incontinence and diarrhoea with increased stimulation = 1/17 (6%) Device removal = 5/17 (29%) Intolerance to VNS therapy = 1/17[b] Following battery depletion, patients elected not to continue VNS therapy = 4/17
(Tanganelli et al 2002)	Level IV case series Quality assessment: Fair	47 patients with medically refractory epilepsy without indication for resective surgery	No adverse events	Skin necrosis requiring revision = 2/47 (4%) Device removal = 3/47 (6%)[ac] Local infection = 1/3 Diffuse pain = 1/3 Generator malfunction (and replaced) = 1/3
(Vonck et al 2004) *Possible overlap with Boon et al (2001) and Boon et al (2002)*	Level IV case series Quality assessment: Fair	118 patients with medically refractory epilepsy who were not suitable candidates for resective surgery Mean age = 32 years (range 4–59)	Bradycardia during intraoperative testing = 1/118 (1%)	Stimulation-related left neck muscle involvement = 2/118 (2%) Gagging = 2/118 (2%) Device removal due to infection = 2/118 (2%)[a]
(Andriola & Vitale 2001)	Level IV case series Quality assessment: Poor	21 patients with developmental disability or mental retardation. Patients had medically refractory epilepsy and were not suitable candidates for resective surgery Age range = 3–56 years	Device removal following post-operative infection = 2/21 (10%)[a]	No adverse events

[a] See Table 15; [b] see Table 22; [c] see Table 13; SD = standard deviation; VNS = vagus nerve stimulation

Table 32 Other adverse events following implantation of VNS system in children

Study	Study design and quality appraisal	Population	Peri-operative adverse events	Adverse events following implantation of VNS system
Partial epilepsies				
(Rychlicki et al 2006) (Zamponi et al 2002)	Level IV case series Quality assessment: Good	36 children with refractory symptomatic or cryptogenic partial epilepsy	No adverse events	Hypertrophic chest scars = 6/36 (17%) Surgical revision due to electrode fracture = 2/36 (6%) Surgical revision due to poor contact between connector pin and generator, as indicated by perceived loss of stimulation = 1/36 (3%) Programmed stimulators lost requiring reprogramming of system = 1/36 (3%) Removal of generator due to lack of efficacy and intolerance = 1/36 (3%) Mild sleep apnoea = 3/36 (8%) Drooling = 1/36 (3%) Snoring = 1/36 (3%)
Generalised epilepsies				
(Parker et al 1999)	Level IV case series Quality assessment: Good	16 consecutive children with cryptogenic epileptic encephalopathy refractory to AED therapy Mean age = 11±3 years	Device removal following infection = 1/16 (6%)[a]	No adverse events
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	No adverse events	Hiccoughs = 4% Insomnia = 2% Ear and jaw pain as stimulation settings increased = 1/50 (2%) Increased salivation = 4/50 (8%) Worsened behaviour or hyperactivity = 3/50 (6%)
Partial and generalised epilepsies				
(Smyth et al 2003)	Level IV retrospective case series Quality assessment: Good	74 consecutive paediatric patients with medically refractory multifocal or generalised epilepsy	Device removal due to infection = 3/74 (4%)[a] Surgical debridement of superficial infection = 1/74 (1%)	Device removal due to device intolerance = 4/74 (5%) Tachycardia = 1/4 Discomfort at stimulator site = 2/4[b] Inactivated device complicating workup of fever = 1/4 Surgical revision due to lead fracture = 2/74 (3%) Outbursts of inappropriate laughter = 1/74 (1%) Intermittent stimulation-induced shoulder adduction = 1/74 (1%) Intermittent torticollis, drooling and urinary

Study	Study design and quality appraisal	Population	Peri-operative adverse events	Adverse events following implantation of VNS system
				retention = 1/74 (1%)
(Lundgren et al 1998a)	Level IV case series Quality assessment: Fair	16 children with intractable epilepsy who had failed intracranial surgery or were not suitable candidates	No adverse events	Aspiration requiring inactivation of stimulator during mealtimes = 2/16 (13%) Surgical revision = 3/16 (19%) Electrode failure = 1/3 Electrode replacement = 1/3 Generator replacement = 1/3 Premature current failure = 2/16 (13%) Increased salivation = 2/16 (13%) Persistent tiredness = 2/16 (13%)
(Nagarajan et al 2002)	Level IV case series Quality assessment: Fair	16 children with medically refractory epilepsy who were unsuitable candidates for intracranial surgery	No adverse events reported	Transient choking episodes = 2/16 (13%) Sore throat despite reduction in VNS settings = 1/16 (6%) Vertigo = 1/16 (6%) Increased drooling = 1/16 (6%) Breathing irregularities during sleep = 3/16 (19%)
(Patwardhan et al 2000)	Level IV case series Quality assessment: Fair	38 consecutive paediatric patients with medically refractory epilepsy *Note: Some of these patients were younger than 2 years old*	No adverse events	Dysautonomia manifested by notable fluctuations in heart rate 6 months after implantation = 1/38 (3%) Raising left arm only when stimulator on = 1/38 (3%) Device removal following infection = 1/38 (3%)[a]
(Saneto et al 2006) *Some subjects are also included in study by Arthur et al (2007)*	Level IV case series Quality assessment: Fair	63 children aged less than 12 years, implanted with VNS	Device failure secondary to loose connection = 1/63 (2%)	No adverse events
(You et al 2007) (Kang et al 2006)	Level IV case series Quality assessment: Fair	28 paediatric patients with medically refractory epilepsy. All patients had either multifocal or generalised epilepsy and were therefore unsuitable candidates for resective surgery	Wound infection requiring revision = 1/28 (4%)	Drooling = 1/28 (4%)
(Alexopoulos et al 2006)	Level IV case series Quality assessment: Poor	46 paediatric patients with medically refractory epilepsy who had failed previous resective surgery or were not suitable candidates ≤12 years: n=21 >12 years: n=25	No adverse events	Device removal following wound infection = 4/46 (9%)[a]
(Blount et al	Level IV case	7 patients with medically	No adverse	Transient oxygen

Study	Study design and quality appraisal	Population	Peri-operative adverse events	Adverse events following implantation of VNS system
2006)	series Quality assessment: Poor	refractory, multifocal, catastrophic epilepsy	events	desaturation after battery replacement = 1/7 (14%)
(Buoni et al 2004a)	Level IV case series Quality assessment: Poor	13 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 17 years (range 6–28)	No adverse events	Intractable headaches = 1/13 (8%) Device removal = 2/13 (15%) lack of clinical benefit = 1/13 skin erosion over generator requiring replacement = 1/13

[a] See Table 15; [b] see Table 13; AED = anti-epileptic drug; VNS = vagus nerve stimulation

Adverse events reported in case reports

Adverse events associated with VNS therapy were also reported in 25 case reports (Appendix E), which described similar events to those reported in the identified studies above. One adverse event which has not previously been reported was a case of a 54-year-old female undergoing surgery for an unrelated procedure (Bernards 2004). In this case report, a laryngeal mask airway was inserted into the patient's airway. Partial obstruction, which was manifested by inspiratory stridor and sternal retractions, was observed to occur simultaneously with the pattern of stimulation.

Summary – Comparative safety of VNS therapy for intractable epilepsy relative to AED therapy alone for adult patients with intractable epilepsy, and AED therapy with or without the ketogenic diet for children.

Thirty-nine studies reported on adverse events associated with VNS therapy in 1,049 patients. Of these, 17 studies reported safety outcomes experienced by children, and 22 studies reported safety outcomes in adults. All were low-level evidence in the form of uncontrolled post-test case series (level IV intervention evidence).

Death following VNS implantation or stimulation was reported in two patients receiving VNS therapy. One patient committed suicide following exacerbation of behavioural and psychiatric disturbances, and the other patient died as a result of aspiration following a generalised tonic-clonic seizure. The contribution of VNS therapy to the deaths of these patients is unknown.

Pain was reported in 5–33% of adults and 5–18% of children. Reporting may have been underestimated in the studies as a number of patients had mental retardation and limited ability to communicate verbally. When pain occurred it was usually as a result of stimulation. In general, this pain was transient, well tolerated or could be resolved through reduction of stimulation parameters. Device removal as a consequence of pain was reported.

Infection occurred both in the immediate post-operative period and in the longer term. The severity of infection ranged from superficial to infections which required device removal. Infection occurred at rates of 2–20% and 3–11% of adults and children, respectively, and

commonly resulted in device removal or surgical revision.

Dysphagia was reported in nine studies at rates of 2–13% in both patient populations. Dysphagia, which may also be pre-existing, is potentially important as it could increase the risk of aspiration.

Paraesthesia was also reported in nine studies at rates of 2–19% and 6–8% in adults and children, respectively. Reported paraesthesia was often mild and well tolerated, tended to be associated with the level of stimulation, and often declined over time.

Secondary safety outcomes of voice alteration and coughing were commonly reported. These events were well tolerated but, if necessary, could generally be resolved through adjustment of the stimulation parameters. In adults, voice alteration was reported in 12–100% and coughing in 4–40% of patients. Children reported voice alteration in 8–53% and coughing in 1–46% of patients. Voice alteration or hoarseness often occurred either immediately following implantation as a result of manipulation of the vagus nerve, or during stimulation, particularly if stimulation parameters had been increased.

Dyspnoea was mainly reported as being evident during physical exertion. If troublesome, patients used the magnet to turn stimulation off during exercise; alternatively, stimulation parameters could be reduced.

Fever, anorexia, vomiting and abdominal pain were not commonly reported adverse events. Other adverse events that occurred included arrhythmias during intraoperative device testing, being reported in two studies and in a number of case reports. Implantation was aborted in a number of case reports following arrhythmias during repeated testing. However, in those patients who proceeded with implantation, no adverse sequelae were reported.

In summary, the majority of adverse events following VNS therapy were of a minor nature. Of these, most were generally well tolerated and did not require device removal.

Is it effective?

Outcomes which were used to assess the effectiveness of VNS plus AED therapy were: epilepsy-related death, quality of life, change in seizure frequency, change in seizure severity, number of patients with 50% or 75% reduction in seizure frequency, change in AED regimen, drop attacks, hospitalisations and functionality of VNS therapy. Epilepsy-related death, quality of life, change in seizure frequency and change in seizure severity were considered to be the primary outcomes for this assessment of effectiveness.

Studies were included in this assessment of the effectiveness of the VNS therapy for epilepsy according to the inclusion criteria, defined a priori, in Box 3 and Box 4.

Box 3 Inclusion criteria for identification of studies relevant to an assessment of effectiveness of VNS therapy for intractable epilepsy in adults

Research question

Is VNS plus AED therapy as effective as, or more effective than, AED therapy alone for adults with intractable epilepsy?

Selection criteria	Inclusion criteria
Population	Adults (>18 years) with intractable epilepsy with previous unsuccessful surgery, or for whom surgery was not suitable
Intervention	VNS therapy adjunctive to AED therapy
Comparator(s)	AED therapy with or without sham intervention
Outcomes	Primary outcomes:
	Epilepsy-related death, quality of life, change in seizure frequency and/or severity in both the short and long term (<3 months and >12 months respectively), drop attacks[a] and numbers of patients with 50% or 75% reduction in seizure frequency and/or severity[a].
	Secondary outcomes:
	Change in dose or frequency of AED use; hospitalisations and continuation rate of VNS therapy.
Study design	Randomised or non-randomised controlled trials, cohort studies, registers, uncontrolled before-and-after case series or systematic reviews of these study designs. Non-systematic reviews; letters; editorials; and animal, in-vitro and laboratory studies were excluded.
Search period	1990 – 10/2007
Language	Studies in languages other than English were only translated and included if they represented a higher level of evidence than that available in the English language evidence-base.

AED = anti-epileptic drug; VNS = vagus nerve stimulation; [a] These outcomes were indicated as secondary outcomes of effectiveness in the protocol for this review; however, based on advice from the Advisory Panel and the MSAC regarding their clinical significance, they have been considered as primary outcomes of effectiveness.

Box 4 Inclusion criteria for identification of studies relevant to an assessment of effectiveness of VNS therapy for intractable epilepsy in children

Research question

Is VNS plus AED therapy as effective as, or more effective than, AED therapy alone, with or without the ketogenic diet, for children with intractable epilepsy?

Selection criteria	Inclusion criteria
Population	Children (>2 years and ≤18 years) with intractable epilepsy with previous unsuccessful surgery, or for whom surgery was not suitable
Intervention	VNS therapy adjunctive to AED therapy
Comparator(s)	AED therapy with or without sham intervention, or ketogenic diet
Outcomes	Primary outcomes:
	Epilepsy-related death, quality of life, change in seizure frequency and/or severity in both the short and long term (<3 months and >12 months respectively), drop attacks[a] and numbers of patients with 50% or 75% reduction in seizure frequency and/or severity[a].
	Secondary outcomes:
	Change in dose or frequency of AED use, hospitalisations and continuation rate of VNS therapy.
Study design	Randomised or non-randomised controlled trials, cohort studies, registers, uncontrolled before-and-after case series or systematic reviews of these study designs. Non-systematic reviews; letters; editorials; and animal, in-vitro and laboratory studies were excluded.
Search period	1990 – 10/2007
Language	Studies in languages other than English were only translated and included if they represented a higher level of evidence than that available in the English language evidence-base.

AED = anti-epileptic drug; VNS = vagus nerve stimulation; [a] These outcomes were indicated as secondary outcomes of effectiveness in the protocol for this review; however, based on advice from the Advisory Panel and the MSAC regarding their clinical significance, they have been considered as primary outcomes of effectiveness.

Forty-nine studies reported on the effectiveness of VNS therapy, including 31 studies of adults and 18 studies of children. Data were extracted into tables (Table 33 – Table 60) detailing the relevant outcomes of effectiveness. Data from studies were entered in a hierarchical manner according to each study's level of evidence, quality assessment, partial epilepsies, generalised epilepsies, partial and mixed epilepsies and, then, in alphabetical order and most recently published. Effectiveness outcomes have been reported in tables according to outcome, and stratified by an adult or child population. If the population studied was a mix of adults and children, the average age of the population was used to determine into which table the study was placed.

Primary effectiveness outcomes

Epilepsy-related death

People with epilepsy have a higher risk of mortality than the general population (Tomson et al 2004). Death can either be directly (sudden unexplained death in epilepsy (SUDEP) or status epilepticus) or indirectly associated with epilepsy.

SUDEP is the occurrence of death without an apparent cause but which is presumed to be related to a person's epilepsy. Six studies were identified which reported epilepsy-related death following VNS therapy (Table 33 and Table 34). No comparative studies reported death following either treatment modality. In non-comparative studies the

incidence of death ranged from 1% to 10% in adults during follow-up periods of up to 6 years. Mortality rates in children ranged from 1% to 4%.

Vonck et al (2004) reported a mortality rate of 1% (1 of 118 patients) following VNS therapy in a fair-quality study (level IV intervention evidence). This was the largest case series which reported epilepsy-related death following VNS therapy and, as such, is likely to report a more accurate mortality rate.

Smyth et al (2003) reported, in a good-quality study, the death of 1 patient in a series of 74 consecutive paediatric patients. This patient died as a result of aspiration following a nocturnal generalised tonic-clonic seizure. This patient's death was also reported in the safety section of this report, where it was stated that it was unclear whether the death was a result of VNS therapy or as a consequence of an increased risk of aspiration in paediatric populations with epilepsy.

Epilepsy-related death was not commonly reported. Without comparative data, it is not possible to determine whether there is an increase or decrease in mortality following VNS plus AED therapy.

Table 33 Change in frequency of epilepsy-related mortality in adults receiving VNS therapy

Study	Study design and quality appraisal	Population	Follow-up period	Frequency of SUDEP
Partial epilepsies				
(Ardesch et al 2007b)	Level IV case series Quality assessment: Fair	19 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Up to 6 years	Possible SUDEP = 1/19 (5%)
(Kawai et al 2002)	Level IV case series Quality assessment: Fair	15 patients with medically refractory partial epilepsy who had failed resective surgery or were not suitable candidates for resective surgery	Median = 56 months (range 48–91)	SUDEP = 1/15 (7%)
(Morrow et al 2000)	Level IV case series Quality assessment: Fair	10 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 32 years (range 16–54)	Mean = 18 months (range 12–36)	SUDEP = 1/10 (10%)
Partial and generalised epilepsies				
(Ben-Menachem et al 1999)	Level IV case series Quality assessment: Fair	64 patients with medically refractory epilepsy who had failed resective surgery or were not suitable candidates for resective surgery	Mean = 20 months (range 3–64)	SUDEP = 1/64 (2%) Death from status epilepticus = 3/64 (5%) Overall: 4/64 (6%)
(Vonck et al 2004) *Possible overlap with Boon et al (2001) and Boon et al (2002)*	Level IV case series Quality assessment: Fair	118 patients with medically refractory epilepsy who were not suitable candidates for resective surgery Mean age = 32 years (range 4–59)	Mean = 33 months (range 6–94)	SUDEP = 1/118 (1%)

VNS = vagus nerve stimulation; SUDEP = sudden unexplained death in epilepsy

Table 34 Change in frequency of epilepsy-related mortality in children receiving VNS therapy

Study	Study design and quality appraisal	Population	Follow-up period	Frequency of death
Partial and generalised epilepsies				
(Smyth et al 2003)	Level IV retrospective case series Quality assessment: Good	74 consecutive paediatric patients with medically refractory multifocal or generalised epilepsy	Minimum = 12 months Mean = 2.2 years	Death due to aspiration secondary to tonic-clonic seizure = 1/74 (1%)
(Alexopoulos et al 2006)	Level IV case series Quality assessment: Poor	46 paediatric patients with medically refractory epilepsy who had failed previous resective surgery or were not suitable candidates ≤12 years: n=21 >12 years: n=25	Median = 2 years	Probable SUDEP = 2/46 (4%)

VNS = vagus nerve stimulation; SUDEP = sudden unexplained death in epilepsy

Quality of life

Measures of quality of life were reported in 15 studies identified in this assessment (Table 35 and Table 36). No comparative studies reported changes in quality of life and the reporting of quality of life measures varied substantially between the included studies. A number of different instruments were used to assess change in quality of life, causing difficulties when comparing results between studies, particularly as not all studies reported the results of statistical testing.

Quality of life outcomes were reported in six studies conducted in adult populations using at least six different instruments. In a good-quality study by Chavel et al (2003) there was statistically significant improvement in quality of life over 24 months in patients with partial epilepsies. The authors noted a pattern of improvement in quality of life in patients who had also reported a reduction in seizure frequency of at least 50%, compared to those patients who did not. The authors acknowledged that the lack of statistical significance could be attributed to the study being underpowered for this outcome.

Similarly, the small study by Morrow et al (2000) reported no improvement in quality of life after 12–36 months of VNS therapy in 10 patients with partial epilepsies using the Rank Health Scale.

McLachlan et al (2003) reported a good-quality study which assessed the quality of life benefits associated with VNS therapy in a cohort of 27 consecutive patients with partial and generalised epilepsies in six centres across Canada. Quality of life was assessed using two instruments—one for patients who had no major cognitive impairment (Quality of Life in Epilepsy Inventory-89, QOLIE-89) and another to be completed by the carers of those with considerable impairments (Epilepsy and Learning Disability Quality of Life, ELDQOL). The QOLIE-89 is a questionnaire which measures health-related quality of life in epilepsy populations, and has previously been validated in a population of

American adults with epilepsy (Devinsky et al 1995). Higher scores in this questionnaire are indicative of a better health-related quality of life. Although a statistically significant improvement was seen in 19 patients who completed the QOLIE-89, only 5 reported what the authors considered to be a clinically relevant improvement in quality of life. It should be noted that, in stating this, the authors did not define what constituted a clinically relevant improvement. Further, of the five patients with a clinically relevant improvement in quality of life, none reported a reduction in seizure frequency of at least 50%. The ELDQOL is a validated instrument for use in children with Lennox-Gastaut syndrome and uses four subscales to report on quality of life in terms of seizure severity, adverse effects, general quality of life and mood. A statistically significant improvement was seen only in the domain relating to seizure severity. The authors did not provide an explanation as to why the greater improvement in adverse effects was not of statistical significance when the lesser improvement seen in seizure severity was.

Change to quality of life was reported in 11 studies of children with epilepsy, all of which were non-comparative (level IV intervention evidence). It is therefore unclear whether the results are caused by the VNS intervention or some other factor.

Change in quality of life in partial epilepsy was reported in one small study of children using the Vineland Behaviour Adaptive Scale (VBAS). The VBAS provides a reliable and valid measure of functional behaviour and grade of personal and social autonomy, and is suitable for use in children with epilepsy. In this good-quality study by Zamponi et al (2002), half of the eight children who completed the VBAS reported no change in quality of life. The remaining patients reported a statistically significant improvement in quality of life but the authors did not indicate whether this was of clinical relevance. There did not seem to be a relationship between those with improved quality of life and those who had a substantial reduction in seizures.

Statistically significant improvements in quality of life were reported in one of three studies of children with generalised epilepsy. In this good-quality study by Parker et al (1999) (level IV intervention evidence) quality of life was assessed using a number of different instruments. Using the Wellcome QOL assessment tool, which was specifically designed for subjects with Lennox-Gastaut syndrome and has good content and construct validity as well as high reliability, the authors reported a statistically significant improvement in both behaviour and perceived side effects of VNS therapy. From the same questionnaire, no statistically significant improvement was reported in the domains of seizure severity, seizure-related injuries, treatment efficacy, mood, overall health, quality of life or anxiety. It is unclear whether the improvement in quality of life seen in this study was of clinical relevance.

Hallbook et al (2005b) assessed quality of life in terms of behaviour, mood, depression and overall quality of life. Questionnaires and visual analogue scales (VAS) were completed by the parents of the patients, usually the mother, except for the depression scale which was completed by the patients. The only statistically significant improvement seen in this series of patients was in overall quality of life (as perceived by the parents). The VAS used to rate quality of life involved a scale ranging from (–10) to (+10), with zero representing no change in quality of life; (–10) was a 100% reduction in quality of life and (+10) represented a 100% improvement in quality of life. There is some uncertainty regarding the reliability of these data as a number of results are outside the scale that was reported to have been used. Attempts to clarify this irregularity with the authors have not been fruitful. No other quality of life instruments used by the authors detected a statistically significant improvement following VNS therapy.

Nagarajan et al (2002) reported quality of life measures in children receiving VNS therapy in an Australian setting. All these children had some degree of mental retardation. Change in quality of life was assessed by asking parents to rate the quality of life of their child using a three-point scale. The majority of parents reported improvement in quality of life, behaviour, alertness and language. The parents of two patients also reported worsened behaviour following VNS therapy.

Reported changes in quality of life were limited for both adults and children. Quality of life ranged from no improvement to moderate improvement in adults and children. Absence of data prevents an accurate assessment of the impact of VNS plus AED therapy on quality of life relative to AED therapy alone (with or without the ketogenic diet in children).

Table 35 Change in quality of life associated with VNS therapy in adults

Study	Study design and quality appraisal	Population	Follow-up period and quality of life tool	Change in quality of life	
				Quality of life scores	**Change from baseline (%)**
Partial epilepsies					
(Chavel et al 2003)	Level IV case series Quality assessment: Good	29 patient with medically refractive partial onset seizures	12–24 months QOLIE-89 Beck Anxiety Inventory (BAI) Beck Depression Inventory (BDI)	QOLIE-89: Scores not reported BAI: Scores not reported BDI: Scores not reported	QOLIE-89: 12 months = NS 24 months = NS BAI: 12 months = NS 24 months = NS BDI: 12 months = NS 24 months = NS
(Morrow et al 2000)	Level IV case series Quality assessment: Fair	10 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Mean = 18 months (range 12–36) Rank Health Scale	No change from baseline	
Partial and generalised epilepsies					
(McLachlan et al 2003)	Level IV case series Quality assessment: Good	27 consecutive patients with medically refractory epilepsy (localised or generalised) who had failed resective surgery or were unsuitable candidates for such surgery	12 months QOLIE-89 Epilepsy and Learning Disability Quality of Life (ELDQOL) 7-point Likert Scale	Baseline: QOLIE-89 = 61 (n=19) ELDQOL (n=7): Seizure severity = 31 Adverse effects = 48 General = 13 Mood = 40 12 months: QOLIE-89 = 67 (n=19) ELDQOL (n=7): Seizure severity = 28 Adverse effects = 41 General = 11 Mood = 40	12 months: QOLIE-89: 10% [95% CI 2.2,10.5] p<0.01[a] ELDQOL: Seizure severity: 10% p<0.05[a] Adverse effects: 15% NS General: -15% NS Mood: No change NS

Study	Study design and quality appraisal	Population	Follow-up period and quality of life tool	Change in quality of life	
				Quality of life scores	**Change from baseline (%)**
				Perception of treatment effect using 7-point Likert scale (n=26): Much worse = 0 Slightly worse = 0 Slightly worse = 1 No change = 3 Slightly improved = 11 Moderately improved = 7 Much improved = 4	
(Chayasirisobhon et al 2003)	Level IV case series Quality assessment: Fair	34 patients with medically refractory epilepsy who were unsuitable for resective surgery	6 months Quality of Life in Epilepsy (QOLIE-10)	Scores not reported	Improved alertness = 19/34 <u>Non mentally retarded patients:</u> Improved alertness and concentration = 8/20 (40%) Improved mood = 3/20 (15%) Improved memory and work performance = 1/20 (5%) <u>Mentally retarded patients:</u> Improved alertness = 11/14 (79%)
(Andriola & Vitale 2001)	Level IV case series Quality assessment: Poor	21 patients with developmental disability or mental retardation. Patients had medically refractory epilepsy and were not suitable candidates for resective surgery	Range = 6 months – 3 years QOL tool not reported	Improvement in mood = >50% of patients (n=21)	

[a] Student's t-test; NS = not statistically significant

Table 36 Change in quality of life associated with VNS therapy in children

Study	Study design and quality appraisal	Population	Follow-up period and quality of life tool	Change in quality of life	
				Quality of life scores	**Change from baseline (%)**
Partial epilepsies					
(Zamponi et al 2002)	Level IV case series Quality assessment: Good	13 children with refractory symptomatic or cryptogenic partial epilepsy	Mean = 13.6 months (range 6–22) Vineland Behaviour Adaptive Scale		Considerable QOL improvement = 1/8 (13%) Moderate QOL improvement = 3/8 (38%) p<0.05 No change in QOL = 4/8 (50%) NS
Generalised epilepsies					
(Majoie et al 2005)	Level IV case series Quality assessment: Good	19 children with childhood epilepsy resembling Lennox-Gastaut syndrome	24 months Independence: Social Functioning scale for the Mentally Retarded[a] Behaviour: Maladaptive Behaviour scale for the Mentally Retarded[a] Mood: Temperament scale for the Mentally Retarded[a]	Baseline: mean±SD Independence = 3.6±1.4 Behaviour = 6.6±1.8 Mood = 7.3±2.9 6 months: Independence = 3.4±1.6 Behaviour = 6.9±2.0 Mood = 7.4±3.5 12 months: Independence = 3.2±1.1 Behaviour = 7.0±2.0 Mood = 7.0±3.3 18 months: Independence = 3.1±1.1 Behaviour = 6.9±1.8 Mood = 7.7±2.6 24 months: Independence = 3.3±1.0 Behaviour = 7.3±1.8 Mood = 7.3±3.0	6 months: NS Independence = –5% Behaviour = +5% Mood = +1% 12 months: NS Independence = –11% Behaviour = +6% Mood = –4% 18 months: NS Independence = –14% Behaviour = +5% Mood = +6% 24 months: NS Independence = –8% Behaviour = +11% Mood = no change
(Parker et al 1999)	Level IV case series Quality assessment: Good	16 consecutive children with cryptogenic epileptic encephalopathy refractory to AED therapy Mean age = 11±3 years	6, 12 and 24 months Vineland Adaptive Behaviour Scale Wellcome QOL Assessment British Picture Vocabulary Scale Leiter International	12 months: Vineland Adaptive Behaviour Scale: No statistically significant change Wellcome QOL Assessment (n=16): Seizure severity = NS Seizure-related injuries = NS Treatment efficacy = NS Treatment side effects = Improved (p<0.05) Behaviour = Improved (p<0.05) Mood = NS Overall health = NS Quality of life = NS	

Study	Study design and quality appraisal	Population	Follow-up period and quality of life tool	Change in quality of life	
				Quality of life scores	**Change from baseline (%)**
			Performance Scale Conner's Parent/Teacher Rating Scale	Worry = NS British Picture Vocabulary Scale (n=6): Improvement p<0.05 Leiter International Performance Scale (n=6): No statistically significant improvement Conner's Parent/Teacher Rating Scale (n=5): No statistically significant improvement 24 months: Vineland Adaptive Behaviour Scale (n=10): No statistically significant improvement	
Partial and generalised epilepsies					
(Hallbook et al 2005b) (Hallbook et al 2005a)	Level IV case series Quality assessment: Fair	15 paediatric patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	9 months Quality of life (QOL): VAS (–10 to +10)[b] Behaviour: Child Behaviour Checklist Mood: Dodrill Mood VAS Depression: Birleson Depression Self-Rating Scale	Baseline (Median (range)): QOL: 10 (10–10)[b] Behaviour: 49 (19–94) Mood: 9 (1–4) Depression: 925 (604–1502) 3 months: QOL: 15 (5–20)[b] Behaviour: 50 (19–102) Mood: 5 (3–15) Depression: 1022 (672–1464) 9 months: QOL: 13 (3–17)[b] p>0.05 Behaviour: 43 (18–92) NS Mood: 6.5 (2–10) NS Depression: 1131 (818–1364) NS	3 months: QOL: +5 (50%) p>0.05 Behaviour: +1 (2%) NS Mood: –4 (–44%) NS Depression: +97 (10%) NS 9 months: QOL: +3 (30%) p>0.05 Behaviour: –6 (–12%) NS Mood: –2.5 (–28%) NS Depression: +206 (22%) NS
(Lundgren et al 1998a)	Level IV case series Quality assessment: Fair	16 children with intractable epilepsy who had failed intracranial surgery or were not suitable candidates	Range 12–24 months VAS (–100 to +100)	Baseline = 0±0 (mean score±SD) 4–6 months: (+)30±32 (n=16)) 10–12 months: (+)33±32 (n=16) 16–18 months: (+)34±36 (n=11) 22–24 months: (+)60±14 (n=2)	4–6 months: +30 (30%)[c] 10–12 months: +33 (33%)[c] 16–18 months: +34 (34%)[c] 22–24 months: +60 (60%)[c]
(Nagarajan et al 2002)	Level IV case series Quality assessment: Fair	16 children with medically refractive epilepsy who were unsuitable candidates for intracranial	Up to 47 months 3-point scale		Quality of life: Improved = 12/16 (75%)[c] Behaviour: Improved = 12/16 (75%)[c]

Study	Study design and quality appraisal	Population	Follow-up period and quality of life tool	Change in quality of life	
				Quality of life scores	**Change from baseline (%)**
		surgery			Worsened = 2/16 (13%)[c] Alertness/awareness: Improved = 15/16 (94%)[c] Language: Improved = 10/16 (63%)[c]
(Patwardhan et al 2000)	Level IV case series Quality assessment: Fair	38 consecutive paediatric patients with medically refractive epilepsy *Note: Some of these patients were younger than 2 years old*	Median = 12 months (range 10–18) VAS (–1 to +1)	Baseline = 0±0 Overall: QOL score = 0.62	Overall: +0.62 (62%) NS
(You et al 2007) (Kang et al 2006)	Level IV case series Quality assessment: Fair	28 paediatric patients with medically refractory epilepsy. All patients had either multifocal or generalised epilepsy and were therefore unsuitable candidates for resective surgery	Mean±SD = 31.4±19.4 months (range 12 months – 7.7 years) Korean version of the Quality of Life in Childhood Epilepsy		Improved memory = 9/28 (32%) Improved mood and alertness = 12/28 (43%) Improved behaviour = 11/28 (39%) Improved achievement = 6/28 (21%) Improved verbal skills = 8/28 (29%)
(Buoni et al 2004a)	Level IV case series Quality assessment: Poor	13 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 17 years (range 6–28)	Mean = 22 months (range 8–36) Parent/caregiver subjective opinion		Improvement in quality of life = 7/13 (54%)

SD = standard deviation; NS = not statistically significant; VAS = Visual Analogue Scale; [a] higher scores indicate better quality of life; [b] scores reported are not consistent with the scale which was reported to be used; [c] no statistical analysis was performed.

Change in seizure frequency

In this assessment of effectiveness, change in seizure frequency has been reported as the average percentage reduction in seizure frequency and was reported in 38 of 49 studies (Appendix F, Table 56 and Table 57). Change in seizure frequency ranged from an increase of 9% to a reduction of 70% at last follow-up in adults, and a reduction of 22–

84% at last follow-up in children. Some caution should be used when considering these ranges, as often a proportion of patients were lost during follow-up, thereby introducing some bias into the results at last follow-up.

Partial epilepsies

In adults with partial epilepsy, change in seizure frequency ranged from an increase of 9% to a reduction of 55% in 14 studies. Figure 6 illustrates the change in mean seizure frequency following VNS plus AED therapy in patients with partial epilepsies.

Clarke et al (1997) reported a good-quality, although small, randomised trial of VNS therapy (high versus low stimulation) in patients with partial epilepsy (level II intervention evidence). Although the study was considered good quality, the authors did not describe the method of randomisation. AED regimens were maintained by all subjects throughout the study. After 12 weeks of VNS therapy, subjects entered into an open-label phase, where all received high stimulation VNS therapy and were followed up until 50 months post-implantation. It should be noted that two subjects received a neurostimulator (Medtronics device Model 7420) other than the NeuroCybernetic Prosthetic device. No additional information regarding the implantation procedure of either device was provided. The authors reported a mean reduction in seizures after the initial 12 weeks of VNS therapy of 50% and 8% for the high and low stimulation (and presumably subtherapeutic) groups, respectively. This indicates that high stimulation VNS therapy provides a considerably greater reduction in seizure frequency compared to low stimulation settings. However, there is some uncertainty surrounding this result as the authors have not reported the baseline seizure frequencies of each group. Without knowledge of the method of randomisation, there is no assurance that both groups were similar at baseline. At 50 months' follow-up the mean ± standard deviation reduction in seizures was 55±39% for nine subjects who completed the follow-up at that time.

Boon et al (2002), in a fair-quality comparative study of VNS plus AED therapy and continuing AED therapy alone (level III-2 intervention evidence) reported on the change in seizure frequency in patients. All the patients in this study were evaluated for their suitability for resective surgery, and were assigned appropriate therapeutic interventions by a multidisciplinary team based on results of long-term video-EEG monitoring, MRI, interictal fluorodeoxyglucose-positron emission tomography (FDG-PET) and neuropsychological examination. As a consequence of this selection method, the mean baseline seizure frequencies of the groups receiving VNS plus AED therapy and AED therapy alone appear to differ greatly (28 and 12 seizures per month, respectively). There was a trend to allocate patients with higher seizure frequencies and hospital admissions to the VNS plus AED group. The large baseline seizure frequency in the VNS group may be attributed to the authors failing to detect a statistically significant difference between the two groups at baseline in terms of seizure frequency. At the end of follow-up the difference in mean reduction in seizures was marked, with the reductions for VNS plus AED therapy and AED therapy alone being 70% and 22%, respectively.

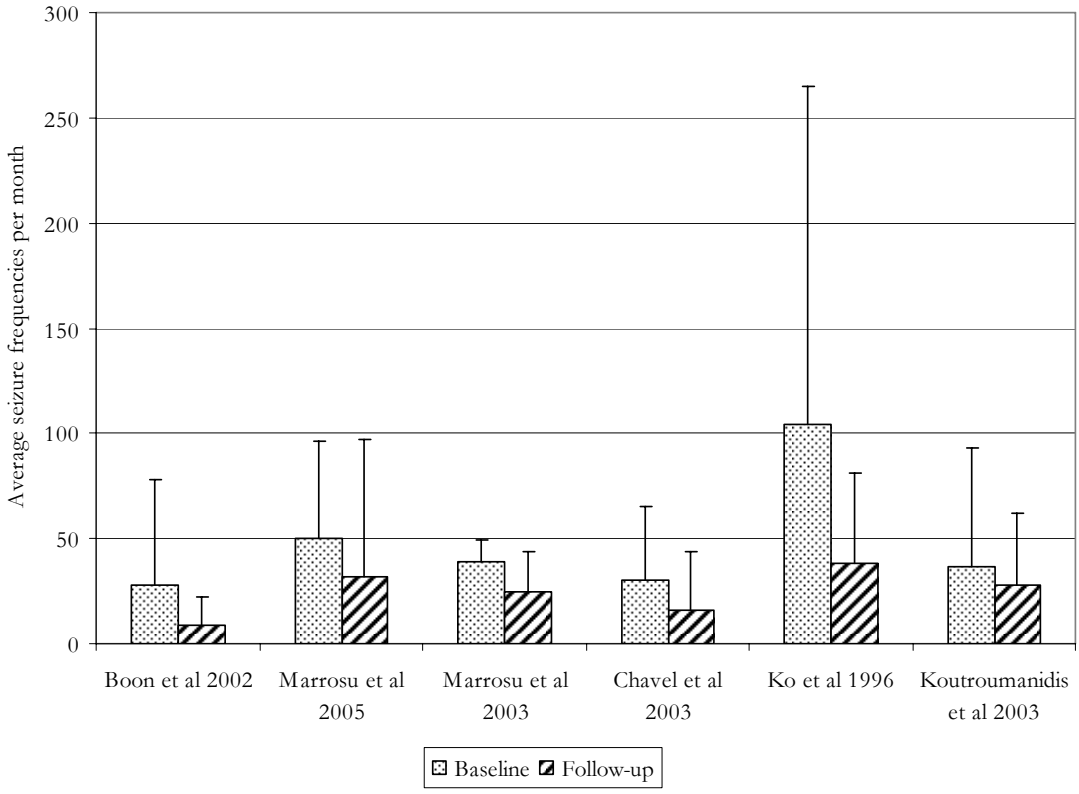
Marrosu et al (2005, 2003) conducted two controlled studies of VNS therapy for partial epilepsy which were of fair quality (level III-2 intervention evidence). The later study compared VNS plus AED therapy to AED therapy alone in adults; however, it is not clear if patients assigned to the control group were necessarily eligible for VNS therapy. In addition, the patients in the control group had been admitted to the Epilepsy Centre for readjustment of their AED therapy and, although medically refractory to AEDs, they had markedly lower seizure frequencies than the VNS group at baseline (4 and 50

seizures per month, respectively). This is likely to explain why the reported results indicate that AED therapy alone was more effective than VNS therapy in reducing seizure frequency (75% and 36%, respectively). Consequently, the results from this study contribute little to resolving whether VNS plus AED therapy is as effective as, or more effective than, AED therapy alone in reducing seizure frequency in medically refractory epilepsy patients. The earlier study assessed the change in seizure frequency in patients with medically refractory complex partial seizures who had received VNS plus AED therapy or had continued AED therapy alone. In this study VNS plus AED therapy resulted in a substantially greater reduction in seizure frequency compared to AED therapy alone (41% and 6%, respectively).

In the study with the longest follow-up (up to 6 years), Ardesch et al (2006) reported the results of VNS therapy in 19 patients with partial epilepsy (level IV intervention evidence). For the first year of follow-up, data from the first 3 months of VNS plus AED therapy was excluded as this was the ramp-up period and was before the most suitable therapeutic settings were determined. The authors reported an improving trend of seizure reduction over the 6-year follow-up period, which was statistically significant after 2 years despite two patients reporting a mild increase in seizure frequency during follow-up. It should be considered that these results are possibly an overestimation of the true change in seizure frequency as the number of patients at the final reported follow-up was notably less than those at early follow-up. The authors had indicated that five patients were lost to follow-up and that two had discontinued VNS therapy due to lack of efficacy.

In the good-quality study by Chavel et al (2003) (level IV intervention evidence) an overall reduction in seizures of 53% and 46% was reported at 12 and 24 months, respectively. Six patients of 29 (21%) failed to complete the follow-up; however, the authors have not indicated whether this was an intention-to-treat or per protocol analysis. As such, there is some degree of uncertainty associated with these results and their interpretation should be cautious. The selection criteria for this study suggested that patients had been excluded as candidates for resective epilepsy surgery. However, it was later reported that two patients withdrew from the study to pursue resective surgery, indicating some inappropriate selection of subjects.

In children with partial epilepsy, a 61% seizure reduction was reported in one good-quality study (level IV intervention evidence) (Zamponi et al 2002).



[a] mean seizure frequencies with standard deviation

Figure 6 Before and after comparison of seizure frequency[a] following VNS plus AED therapy in adults with partial epilepsy

Generalised epilepsies

In adult patients with generalised epilepsies, reduction in seizure frequency was in the range 43–61%. No comparative studies in patients with generalised epilepsies were identified. Figure 7 indicates the change in mean seizure frequency for adults with generalised epilepsies who received VNS plus AED therapy.

The fair-quality study by De Herdt et al (2007) (level IV intervention evidence) assessed the impact of VNS therapy on seizure frequency in 138 consecutive patients with medically refractory epilepsy who were unsuitable candidates for resective surgery. This study analysed the data to compare the effectiveness of VNS therapy in adults and children, and in partial epilepsy and generalised epilepsy. The findings of the study were that VNS plus AED therapy was able to achieve an overall reduction in seizure frequency of 51%. Reduction in seizure frequency was greater in adults than children (53% and 41%, respectively). Seizure frequency was reduced more in patients with symptomatic generalised epilepsy than those with partial epilepsy (56% and 50%, respectively). Unfortunately, the baseline seizure frequencies of the groups were dissimilar; therefore, subsequent comparison is likely to be problematic.

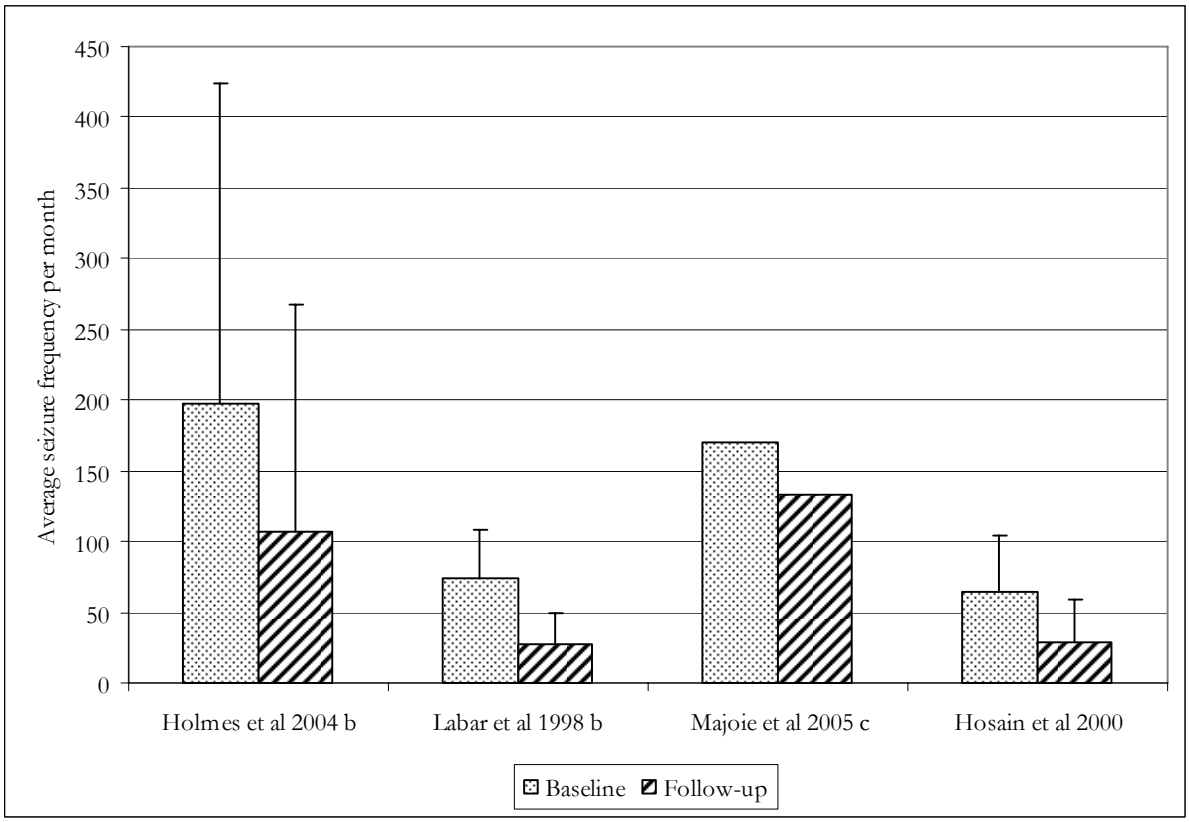
Mean reduction in seizure frequency in children with generalised epilepsies ranged from 22% to 58% (Figure 7). In the three studies which reported on the effectiveness of VNS therapy in children with Lennox-Gastaut syndrome, the mean reduction in seizure

frequency also ranged from 22% to 58% (Frost et al 2001; Hosain et al 2000; Majoie et al 2005).

Saneto et al (2006) reported on a group of 63 children (aged less than 12 years) with pharmacoresistant epilepsy who were unsuitable candidates for resective epilepsy surgery. Of the 43 children who provided data on seizure frequency following VNS plus AED therapy, an overall median reduction in seizure frequency of 84% was reported. The quality of this study was weakened by the retrospective nature of data collection, which relied on chart review of clinic visits before and after VNS implantation. The authors did not report the use of seizure diaries to collect data pertaining to seizure frequency, nor was there a baseline period before implantation to establish seizure frequency. These flaws in study design would all contribute to uncertainty in the results.

Parker et al (1999) reported the effect on seizure frequency of VNS in a paediatric population of 16 patients with cryptogenic epileptic encephalopathies. At 6, 12 and 24 months the reductions in seizure frequency were 8%, 14% and 43%, respectively. It should be noted, however, that the 24 months follow-up data were not analysed according to intention to treat and therefore may not be truly reflective of the average reduction in seizure frequency.

Alexopoulos et al (2006) reported the effects of VNS therapy in a cohort of 46 paediatric patients. This evaluation was based on a retrospective review of chart records of patients who underwent left VNS implantation between December 1997 and December 2003. Data pertaining to seizure frequency was obtained from medical records of patients' annual visits, using standardised seizure frequency forms as opposed to seizure diaries. Median seizure frequency reduction, as shown in Table 56, increased as duration of VNS therapy increased. However, this analysis is based on censored data with declining numbers as follow-up progressed.



[a] mean seizure frequencies with standard deviation; [b] studies conducted in adult populations; [c] standard deviation not reported

Figure 7 Before and after comparison of seizure frequency[a] following VNS plus AED therapy in adults or children with generalised epilepsy

Comparative data reported changes in seizure frequency for VNS plus AED therapy and AED therapy alone of 36–50% and 6–75%, respectively. In considering these data, it is important to note that some comparative studies had flaws in their study design. Results from case series generally showed a reduction in seizure frequency following VNS implantation.

Number of patients with 50% or 75% reduction in seizure frequency and/or severity

It is widely accepted that a reduction in seizure frequency of at least 50% is a clinically relevant outcome for epilepsy patients. As such, most studies refer to patients with a 50% or greater reduction in seizure frequency as being responders and those with a lesser reduction as being non-responders. Forty-one studies were identified as meeting the inclusion criteria of this assessment and providing data to allow reporting of reductions in seizure frequency of greater than 50% (Appendix F, Table 58 and Table 59).

Two comparative studies in partial epilepsies (level III-2 intervention evidence) by the same investigators have reported the number of patients who responded with a greater than 50% reduction in seizure frequency following VNS plus AED therapy (Marrosu et al 2003, 2005). As indicated previously, baseline seizure frequencies in the later study were distinctly different between the VNS plus AED group and those receiving AED therapy alone. The VNS group had markedly more severe epilepsy (in terms of refractory seizure frequency) than the AED group. Consequently, comparison between the two groups is problematic and the results of this study should not be considered to be reflective of a true comparison. In the earlier study by Marrosu et al (2003), VNS plus AED therapy showed substantially more patients achieving a 50% or greater reduction in seizure frequency compared to AED therapy (40% and zero, respectively).

In adult patients with partial epilepsies the proportion of responders (≥50% reduction in seizure frequency) ranged from 19% to 60% of patients. Similar results were obtained in patients with generalised epilepsies, where the number of responders ranged from 33% to 67%.

In children with epilepsy the proportion of responders ranged from zero to 68% of patients (level IV intervention evidence). No comparative studies of the efficacy of VNS therapy in children relative to AED therapy or the ketogenic diet were identified.

Only one study reported the number of responders in children with partial epilepsy. In this small but good-quality study, the number of children with greater than or equal to 50% reduction in seizure frequency was 75% (Zamponi et al 2002).

In children with generalised epilepsy, the number of responders ranged from 21% to 63% (level IV intervention evidence). Interestingly, the greatest proportion of responders was seen in a study of children with Lennox-Gastaut syndrome (Frost et al 2001).

Arthur et al (2007) considered the effectiveness of VNS therapy in a small group of children with epilepsy resulting from mitochondrial disorders. This fair-quality study was a retrospective chart review and reported the number of children who obtained a 50% or greater reduction in seizure frequency following VNS therapy. The authors reported little change in seizure frequency during follow-up, which ranged from 12 to 48 months, and no child obtained a reduction in seizure frequency of 50% or greater.

Nagarajan et al (2002) reported that 10 of 16 (63%) children implanted with VNS in an Australian hospital had a reduction in seizure frequency of at least 50% following implantation. Of these, nine achieved at least a 75% reduction in seizure frequency.

As reported by the more reliable of the comparative studies, VNS plus AED therapy provides greater achievement of a 50% reduction in seizure frequency than AED therapy alone. In children the number of responders ranged from zero to 68%.

Change in seizure severity

As well as reducing seizure frequency, VNS therapy may also provide relief in terms of severity of seizures and post-ictal recovery. Unfortunately, changes in seizure severity were, for the most part, reported subjectively by patients, and thus there are difficulties in quantifying any change. However, a reduction in seizure severity was reported in 19–50% of adults and 25–63% of children (Table 37 and Table 38).

Only one study in adults reported the change in seizure severity using a validated seizure severity assessment tool (Table 37). Morrow et al (2000) (level IV intervention evidence) assessed any change in seizure severity in partial epilepsies following VNS therapy by use of the Liverpool Seizure Severity Scale, which considers the perception of control and also ictal/post-ictal events (Baker et al 1991). In the eight patients who completed this questionnaire, there was a statistically significant reduction in the severity of the ictal phase of major seizures.

Two studies in children reported change in seizure severity using the National Hospital seizure severity scale (NHS_3 (O'Donoghue et al 1996)) (Table 38). This NHS_3 tool assigns a score of 0–4 for six questions, and 0–2 for one question, for each seizure type experienced (except myoclonic or absence seizures). The questions indicate whether a generalised seizure has occurred; if the patient has fallen to the ground; whether injuries, automatisms or incontinence occurred; if the patient was aware of a warning in sufficient time to protect themself; and the time taken for the patient to recover from the seizure. A reduction in score using this scale indicates an improvement in seizure severity.

Lundgren et al (1998) (level IV intervention evidence) reported the change in seizure severity following VNS therapy in a paediatric population also using the NHS_3 tool. The reported effect on seizure severity at 24 months may not be entirely reflective of the population studied as five patients discontinued VNS therapy after 12 months due to a lack of clinical benefit. As such, the change in seizure severity at 12 months, where there was an improvement in seizure severity of 20% for all 16 patients, may be more indicative of the effect of VNS plus AED therapy on seizure severity.

In the fair-quality study by Hallbook et al (2005b) (level IV intervention evidence) 15 paediatric patients were studied for 9 months following VNS therapy. All 15 patients

reported a median improvement of 25% in seizure severity according to the NHS_3 questionnaire.

Table 37 Change in seizure severity following VNS therapy in adults

Study	Study design and quality appraisal	Population	Follow-up period and seizure severity tool	Change in severity of seizures
Partial epilepsies				
(Ardesch et al 2007b)	Level IV case series Quality assessment: Fair	19 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Up to 6 years	Reduced severity = 9/19 (47%)
(Koutroumanidis et al 2003)	Level IV case series Quality assessment: Fair	16 patients with medically refractory complex partial epilepsy who have failed previous resective surgery Mean age ± SD = 36±11.5 years (range 12–39)	Mean±SD = 14±9 months (range 3–36)	Reduced severity = 3/16 (19%) Increased severity = 1/16 (6%)
(Morrow et al 2000)	Level IV case series Quality assessment: Fair	10 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 32 years (range 16–54)	Mean = 18 months (range 12–36) Liverpool Seizure Severity Scale	Reduced ictal phase of major seizures (n=8) $p<0.05$[a]
Partial and generalised epilepsies				
(Ben-Menachem et al 1999)	Level IV case series Quality assessment: Fair	64 patients with medically refractory epilepsy who had failed resective surgery or were not suitable candidates for resective surgery	Mean = 20 months (range 3–64)	Partial epilepsy: >50% reduction in severity = 19/47 (40%) Generalised epilepsy: Not reported Lennox-Gastaut syndrome: 25% reduction in severity = 3/8 (38%) 50% reduction in severity = 1/8 (13%)

[a] Wilcoxon Signed Rank test; VNS = vagus nerve stimulation

Table 38 Change in seizure severity following VNS therapy in children

Study	Study design and quality appraisal	Population	Follow-up period and seizure severity tool	Change in severity of seizures	
				Severity scores	**Absolute change (% change)**
Partial and generalised epilepsies					
(Hallbook et al 2005b) (Hallbook et al 2005a)	Level IV case series Quality assessment: Fair	15 paediatric patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	9 months National Hospital Seizure Severity Scale (NHS_3)	Baseline (median): 12 (range 4–19) 3 months: 9 (range 1–19) p<0.001[a] 9 months: 9 (range 1–16) p<0.001[a]	3 months: 3 (25%) 9 months: 3 (25%)
(Lundgren et al 1998a)	Level IV case series Quality assessment: Fair	16 children with intractable epilepsy who had failed intracranial surgery or were not suitable candidates	Range 12–24 months National Hospital Seizure Severity Scale (NHS_3)	Baseline (Mean±SD): 15±5 (n=16) 4–6 months: 12±5 (n=16) 10–12 months: 12±5 (n=16) 16–18 months: 11±6 (n=11) 22–24 months: 10±8 (n=2)	4–6 months: 3 (20%) 10–12 months: 3 (20%) 16–18 months: 4 (27%) 22–24 months: 5 (33%)
(Nagarajan et al 2002)	Level IV case series Quality assessment: Fair	16 children with medically refractive epilepsy who were unsuitable candidates for intracranial surgery	Up to 47 months		Reduced severity = 10/16 (63%) Increased severity = 1/16 (6%) Severity unchanged = 4/16 (25%)

VNS = vagus nerve stimulation

Change in seizure severity was difficult to quantify. Seizure severity following VNS plus AED therapy was reduced by 19–50% in adults and 2–63% in children.

Drop attacks

Drop attacks in epilepsy are particularly important because of the associated risk of injury, with patients often requiring a helmet and constant monitoring to avoid serious injury (Tinuper et al 1998). Drop attacks can be seen in generalised epilepsies with atonic, tonic-clonic or myoclonic-astatic seizures. People with partial epilepsies may also experience drop attacks due to secondary generalisation (Tinuper et al 1998). Expert opinion indicates that a reduction in the frequency of drop attacks would be of considerable clinical importance, more so than a reduction in other seizure types (expert opinion of MSAC Advisory Panel, 2008).

Reports of changes in the frequency of drop attacks were limited to seven studies, all of which were level IV intervention evidence (Table 39 and Table 40). Many studies reported change in frequency of atonic seizures, with only three studies specifically

reporting drop attacks in general. Decreases in frequency of drop attacks or seizures ranged from zero to 99%.

Casazza et al (2006) reported on 17 patients, of which 16 had previously reported drop attacks. A reduction in drop attacks was seen in 11 of 16 patients (69%), with 6 of these patients reporting a reduction of between 20% and 50%. An increase in drop attacks was also reported in 5 of 16 (31%) patients. The majority of these patients reported an increase of between 20% and 50%, although one patient reported an increase in drop attacks of more than 75%.

In children, frequency of drop attacks was reported in only two studies. Frost et al (2001) reported the change in frequency of drop attacks over the first 6 months of VNS therapy in 50 patients with Lennox-Gastaut syndrome. By the end of this period, 24 patients had reported a median reduction of 88% in drop attacks ($p<0.05$).

Patwardhan et al (2000) reported a reduction of 80% in atonic seizures following 12 months of VNS therapy. The authors did not indicate if this figure was an average or if a reduction was seen in all patients.

A reduction in drop attacks is considered a highly clinically important outcome. Limited reporting of small groups reported a reduction in drop attacks of between zero and 99%.

Table 39 Change in drop attacks associated with VNS therapy in adults

Study	Study design and quality appraisal	Population	Follow-up period	Change in frequency of drop attacks (as a percentage of baseline drop attack frequency)
Partial epilepsies				
(Koutroumanidis et al 2003)	Level IV case series Quality assessment: Fair	16 patients with medically refractory complex partial epilepsy who have failed previous resective surgery Mean age ± SD = 36 ±11.5 years (range 12–39)	Mean±SD = 14±9 months (range 3–36 months)	Drop attacks: 0% (n=1)
Generalised epilepsies				
(Holmes et al 2004)	Level IV case series Quality assessment: Good	16 patients with IGE or SGE aged 12 years or older	12–21 months	Atonic seizures: Median = 99% (range 67–100%) (n=3) p=0.25[a]
Partial and generalised epilepsies				
(Ben-Menachem et al 1999)	Level IV case series Quality assessment: Fair	64 patients with medically refractory epilepsy who had failed resective surgery or were not suitable candidates for resective surgery	Mean = 20 months (range 3–64)	Atonic seizures: LGS: Mean = 10±31% (n=7)
(Casazza et al 2006)	Level IV case series Quality assessment: Fair	17 adult patients with medically refractory epilepsy who had previously failed resective surgery or were not suitable candidates 16 patients with drop attacks	Range 4–9 years	Reduction in drop attacks: <20% = 2/16 (13%) 20–50% = 6/16 (38%) 50–75% = 2/16 (13%) >75% = 1/16 (8%) Increase in drop attacks: 20–50% = 4/16 (25%) 50–75% = 0/16 (0%) >75% = 1/16 (8%)
(Chayasirisobhon et al 2003)	Level IV case series Quality assessment: Fair	34 patients with medically refractory epilepsy who were unsuitable for resective surgery Mean age = 27.6 years (range 5–70)	6 months	Atonic seizures: Mean = 95±3.2% (n=3)

[a] Wilcoxon's signed rank test; SD = standard deviation; VNS = vagus nerve stimulation; LGS = Lennox-Gastaut syndrome

Table 40 Change in drop attacks associated with VNS therapy in children

Study	Study design and quality appraisal	Population	Follow-up period	Change in frequency of drop attacks (as a percentage of baseline drop attack frequency)
Generalised epilepsies				
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	Range 1–6 months	Drop attacks 1 month: Median = 47% (n=46) p<0.0001[a] 3 months: Median = 55% (n=43) p<0.0001[a] 6 months: Median = 88% (n=24) p=0.0002[a]
Partial and generalised epilepsies				
(Patwardhan et al 2000)	Level IV case series Quality assessment: Fair	38 consecutive paediatric patients with medically refractory epilepsy *Note: Some of these patients were younger than 2 years old*	Median = 12 months (range 10–18)	Atonic seizures: 80% (n=17)

[a] Wilcoxon's signed rank test; SD = standard deviation; IGE = idiopathic generalised epilepsy; SGE = symptomatic generalised epilepsy; VNS = vagus nerve stimulation

Secondary effectiveness outcomes

Change in anti-epileptic drug usage following VNS therapy

An additional benefit of VNS therapy may be the reduction in the number or dose of AEDs required to control a patient's seizures. This would be beneficial for a number of reasons including minimising the risk of unpleasant side effects which are often associated with AEDs.

Although a number of studies did not allow changes to AED treatment regimens so as to ensure that benefits seen during the study were attributable to VNS therapy, 10 studies did report changes to AED regimens as a consequence of VNS therapy (Table 41 and Table 42).

Effects on AED regimens ranged from increasing either the number or dose of AEDs to decreasing the number of AEDs required to maintain seizure control.

In adults two studies (level IV intervention evidence) reported changes to AED therapy in patients with partial epilepsies. The number or dose of AEDs was decreased in 5% and 38% of patients, respectively, in the studies reported by Ardesch et al (2007) and Kawai et al (2002). An increase to either the number or dose of AEDs was reported in 15% and 21% of patients, respectively.

Only one study (level IV intervention evidence) of patients with generalised epilepsy reported changes to AED therapy. In this study by Kostov et al (2007) a mean reduction from 2.3 to 1.7 AEDs was seen over an average of 23 months. This reduction, however, was not of statistical significance.

In children three studies reported changes to the number or dose of AEDs used. In the study by Hosain et al (2000) changes to AED therapy were only allowed after the first five patients. At 2 months follow-up, AED use was reduced by one agent in six of eight patients in whom AED changes were allowed.

Nagarajan et al (2002) reported a small increase in the median number of AEDs used; however, it is unclear whether this was of statistical or clinical importance.

No studies reported a statistically significant change in AED usage (either dose or number of AEDs) following VNS implantation.

Table 41 Change in anti-epileptic drug (AED) usage following VNS therapy in adults

Study	Study design and quality appraisal	Population	Follow-up period	AED usage	
				At baseline	At follow-up
Partial epilepsies					
(Ardesch et al 2007b)	Level IV case series Quality assessment: Fair	19 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Up to 6 years	Not reported	Increased AED = 4/19 (21%) Reduced AED = 1/19 (5%)
(Kawai et al 2002)	Level IV case series Quality assessment: Fair	15 patients with medically refractory partial epilepsy who had failed resective surgery or were not suitable	Median = 56 months (range 48–91)	Range 2–5	Number and dose decreased = 2/13 (15%) Dose only decreased = 3/13 (23%) No change = 6/13 (46%) Number or dose increased = 2/13 (15%)
Generalised epilepsies					
(Kostov et al 2007)	Level IV case series Quality assessment: Fair	12 patients with medically refractory idiopathic generalised epilepsy Mean age±SD = 31±14 years (range 11–48)	Mean = 23 months (range 9–54)	Mean AED = 2.3	Mean AED = 1.7 NS
Partial and generalised epilepsies					
(McLachlan et al 2003)	Level IV case series Quality assessment: Good	27 consecutive patients with medically refractory epilepsy (localised or generalised) who had failed resective surgery or were unsuitable candidates for such surgery Mean age = 30 years (range 12–46)	12 months	Not reported	No change but dosage had decreased in 43% of patients
(De Herdt et al 2007) *Possibly some overlap of patients with Boon et al (2001) and Boon et al (2002)*	Level IV case series Quality assessment: Fair	138 consecutive patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 30±13 years (range 4–59)	Mean = 44±27 months (range 12–120)	Mean = 3 (range 1–5)	Mean = 3 (range 0–5)
(Vonck et al 2004) *Possible overlap with Boon et al (2001) and Boon et al (2002)*	Level IV case series Quality assessment: Fair	118 patients with medically refractory epilepsy who were not suitable candidates for resective surgery Mean age = 32 years (range 4–59)	Mean = 33 months (range 6–94)	Mean = 3 (range 1–5)	Mean = 3 (range 1–5) 1 AED tapered = 8/118 (7%) 2 AEDs tapered = 1/118 (1%)
(Andriola & Vitale 2001)	Level IV case series	21 patients with developmental disability or mental retardation.	Range = 6 months – 3 years	Mean = 2.8 (range	AEDs reduced by 1 = 34%

Study	Study design and quality appraisal	Population	Follow-up period	AED usage	
				At baseline	At follow-up
	Quality assessment: Poor	Patients had medically refractory epilepsy and were not suitable candidates for resective surgery Age range = 3–56 years		1–4)	AEDs increased by 1 = 3/21 (14%)

VNS = vagus nerve stimulation; AED = anti-epileptic drug; SD = standard deviation; NS = not significant

Table 42 Change in anti-epileptic drug (AED) usage following VNS therapy in children

Study	Study design and quality appraisal	Population	Follow-up period	AED usage	
				At baseline	At follow-up
Generalised epilepsies					
(Hosain et al 2000)	Level IV case series Quality assessment: Fair	13 patients with Lennox-Gastaut syndrome Median age = 13 years (range 4–44)	6 months	Median = 6 AEDs (range 4–12)	At 2 months: In 6 of 8 patients, AED use was reduced by 1 agent
Partial and generalised epilepsies					
(Nagarajan et al 2002)	Level IV case series Quality assessment: Fair	16 children with medically refractory epilepsy who were unsuitable candidates for intracranial surgery	Up to 47 months	Median = 2.5 (range 1–4)	Median = 3 (range 2–4)

Hospitalisations

A potential benefit of VNS therapy in terms of effectiveness (and cost-effectiveness) is a reduction in the time spent in hospitalised care. This outcome was reported in one fair-quality study conducted by Boon et al (2002) (level III-2 intervention evidence).

In this study the authors compared measures of effectiveness in patients receiving VNS plus AED therapy with those receiving continued AED therapy. All patients had undergone evaluation for resective surgery and had been found to be unsuitable candidates; however, it is not known if those patients who continued to receive AED therapy were also suitable for VNS therapy. Hospital admission days were recorded during a mean follow-up period of 26 months. Following VNS therapy, there was a reduction in hospital admission days of 78%; this is compared to an increase of 18% in hospital admission days in patients receiving only AED therapy. With this comparison it is important note that the baseline figure for admission days were not similar between the two groups; therefore, these results may not be truly reflective of the change that would be seen.

Comparison of VNS plus AED therapy with AED therapy alone in adults resulted in a reduction in hospitalisations of 78% and an increase of 18%, respectively. These data are limited by discrepancies at baseline between the two study groups.

Continuation rate of VNS therapy

In this assessment the continuation rate of VNS therapy has been defined as the number of patients still receiving VNS therapy at the end of follow-up. To no longer be considered to be receiving VNS therapy, either the patient must have had the device deactivated and no longer be receiving stimulation, or the device must have been explanted.

Data pertaining to the continuation rate of VNS therapy was extracted from 41 studies and calculated to range from 29% to 100% (Appendix F, Table 60 and Table 61). In adults 9 of 28 (32%) studies reported the continuation rate of VNS therapy to be 100%; in children this outcome was reported in 5 of 13 (38%) studies. The chief reason for no longer continuing to receive VNS therapy was lack of clinical efficacy.

In the comparative study by Marrosu et al (2003) (level III-2 intervention evidence) no discontinuation of therapy was reported for patients receiving either VNS or AEDs. This study had a follow-up period of 12 months, during which no change to the AED regimen was made.

In the fair-quality study by Casazza et al (2006) the authors reported that at the end of follow-up only five (29%) patients continued to receive VNS therapy. This study had the longest follow-up period of all the included studies, with patients being followed for 4–9 years. It is interesting to note that, in two patients who had battery depletion and elected to have the device explanted, the effect of VNS was maintained. In this study only 4 of 17 patients (24%) reported a seizure reduction of greater than 50%, and 16 of the 17 suffered from drop attacks. The poor response in terms of seizure reduction was the primary reason for patients discontinuing stimulation.

Alexopoulos et al (2006) reported that VNS discontinuation occurred in 9 of 46 patients (20%). This was the result of six patients ceasing stimulation due to lack of clinical benefit; of these, three VNS devices were eventually removed. The family of one patient elected not to have the generator replaced at the end of battery life, and four devices were removed due to infection although one was subsequently replaced.

Chavel et al (2003) reported on 23 of 29 (79%) patients still receiving VNS therapy at the end of the 24-month follow-up. The reason for some of the withdrawal may be explained by inappropriate subject selection as two patients withdrew to pursue resective surgery. Another patient died from unrelated causes and another was lost to follow-up due to unrelated illness.

In the study by Kawai et al (2002) 78% (10 of 13 patients) of the study population elected to continue VNS therapy. Two patients elected to discontinue therapy and have the generators removed due to a lack of clinical effectiveness. Another patient elected to undergo further resective surgery (after having failed two previous resections) and became subsequently free of seizures.

Continuation of VNS therapy varied greatly between studies (29–100%) and was closely associated with perceived clinical benefit.

Summary – Comparative effectiveness of VNS plus AED therapy relative to AED therapy alone in adults with refractory epilepsy, and AED therapy with or without the ketogenic diet in children.

Effectiveness of VNS therapy in epilepsy has been assessed in terms of mortality associated with epilepsy, change in seizure frequency or severity, impact on quality of life and changes to AED regimens and hospitalisations.

No comparative studies were identified which studied the effectiveness of VNS plus AED therapy relative to AED therapy with or without the ketogenic diet in children.

Primary effectiveness outcomes

Death from epilepsy-related causes (in particular SUDEP) was reported in seven studies. The incidence of death ranged from 1% to 10% in adults and 1% to 4% in children, and was mainly reported to be (possible) SUDEP. No comparative studies reported epilepsy-related death; therefore, it is difficult to determine the impact of VNS therapy on this outcome.

Assessment of changes in quality of life following VNS plus AED therapy was problematic due to the number of differing instruments used to detect any changes and the lack of any comparison with AED therapy alone. Improvements in quality of life of adults from baseline was limited and ranged from no improvement to modest improvement. One study which reported a statistically significant improvement in quality of life indicated that only a small proportion of patients (23%) in whom an improvement was seen reported a change that was of clinical relevance (McLachlan et al 2003).

Reported changes in quality of life in children following VNS plus AED therapy were similar to those of adults in that they were limited and modest improvements.

The effectiveness of VNS plus AED therapy, in terms of seizure reduction, appears to be greater than that of AED therapy alone. Two of four identified studies reported greater seizure reduction with VNS plus AED therapy (41–50%) compared with AED therapy alone (6–8%) (Clarke et al 1997; Marrosu et al 2003). The other two studies were compromised by selection bias within the comparative group. Patients receiving AED therapy in the study by Marrosu et al (2005) were not eligible for VNS plus AED therapy. This was highlighted by the difference in baseline seizure frequency. Similarly, in the study by Boon et al (2002), treatment assignment was conducted by a multidisciplinary team who allocated treatments according to their opinion as to which treatment was likely to provide the better outcome. These two studies are unlikely to truly reflect the comparative seizure frequency of VNS plus AED therapy versus AED therapy alone in this population and, as such, the results should be disregarded.

In addition to the average change in seizure frequency seen in patients, two comparative studies (level III-2 intervention evidence) reported on the number of patients (responders) who achieved at least a 50% reduction in seizure frequency. The proportion of responders in the VNS plus AED and AED alone groups in the studies by Marrosu et al (2003 and 2005) were 27% and 80%, and 40% and 0%, respectively. Again, the selection bias apparent in the AED group of the 2005 study limits the interpretation of the results, and the results of the

earlier (2003) study should be considered to be more indicative of a true comparison.

Change in seizure severity was reported in seven non-comparative studies (level IV intervention evidence) and in only one study of adults using a validated assessment tool. In this fair-quality study by Morrow et al (2000) a statistically significant reduction in the severity of the ictal phase of major seizures was reported but the reduction was not quantified.

In two studies of children the National Seizure Severity Scale was used to determine changes in seizure severity. Improvements in severity after 9 and 12–24 months were reported to be 25% and 33%, respectively (Hallbook et al 2005b; Lundgren et al 1998a). In the study by Nagarajan et al (2002), which was conducted in an Australian setting, reduced severity of seizures was subjectively reported in 63% of patients.

The effect of VNS therapy on drop attacks was reported in seven low-level evidence studies (level IV intervention evidence). Four of these studies reported drop attacks in a very small number of patients; however, three studies reported the effect of VNS therapy in more than 10 patients (Casazza et al 2006; Frost et al 2001; Patwardhan et al 2000). Cassaza et al (2006) reported a 20–50% reduction in drop attack in 6 of 16 (38%) adults. In addition, 4 of 16 (25%) adults reported an increase of 20–50% in drop attacks and one patient (8%) reported an increase of more than 75%. In children two studies reported sizeable reductions in drop attacks following VNS therapy. Frost et al (2001) reported an 88% reduction in attacks at 6 months ($p<0.0001$). Additionally, Patwardhan et al (2000) reported an 80% reduction in atonic seizures following 12 months of therapy.

Secondary effectiveness outcomes

Change in hospitalisations following VNS or AED therapies were compared in one study. A reduction in hospital admission days of 78% was seen in the group receiving VNS plus AED therapy compared with a reduction of 18% for the group receiving AED therapy alone (Boon et al 2002). As previously suggested, there are some limitations with this study, and therefore the results should be considered with caution.

Changes in AED regimen (either number or dosage) as a result of VNS therapy were reported in level IV intervention evidence. Although both reductions and increases in AEDs were reported, no studies reported changes to AEDs that were of statistical significance in adults or children, nor was it clear if any changes were clinically relevant.

Data regarding the continuation rate of VNS therapy were extracted from 41 studies. The continuation rate ranged from 29% to 100%. The rate of VNS plus AED therapy and AED therapy alone were both reported as 100% over 12 months (Marrosu et al 2003). The study with the longest follow-up period of 4–9 years reported functionality of VNS therapy as 29%, with the primary reason for discontinuation being lack of clinical benefit.

To summarise, VNS plus AED therapy may provide a statistically significant reduction in seizure frequency in some patients. Clinically relevant reductions in seizure frequency are likely to be seen in 41–50% of patients. Moderate changes in quality of life have been demonstrated in some patients; however, no statistically significant changes in the usage of AEDs were reported. Benefits to patients in terms of reducing drop attacks are more likely to be seen in children than adults. Continuation of VNS therapy looks to be closely associated with a perceived clinical benefit.

Discussion of safety and effectiveness

Safety

The comparative safety of VNS plus AED therapy relative to either AED therapy alone in adults, or AED therapy with or without the ketogenic diet in children, has not been reported in the literature.

The low-level evidence available regarding adverse events associated with VNS therapy is notable in that they report complications associated with VNS implantation and stimulation. These would be **in addition** to complications that may be associated with AED therapy (with or without the ketogenic diet).

There did not appear to be any difference in frequency of adverse events between patients with partial or generalised epilepsy.

Complications associated with VNS therapy were, for the most part, reasonably well tolerated by patients and often resolved with time or a reduction of stimulation parameters. Complications either resulted from the implantation procedure or were associated with stimulation by the VNS device.

Patients with epilepsy, particularly children and those with uncontrolled epilepsy, have a higher risk of death than the general healthy population (Tomson et al 2004). In the assessment of the safety of VNS therapy, it is important to distinguish between death that is directly or indirectly a result of seizures or the pre-existing epilepsy (eg status epilepticus or SUDEP) and that which is related to the therapy. Due to the uncontrolled nature of the studies which reported death in patients receiving VNS plus AED therapy, it is difficult to attribute the cause of death to VNS therapy. Two deaths were reported during VNS plus AED therapy, one as a result of aspiration following a seizure in a paediatric patient and the other as a result of exacerbated psychiatric symptoms which prompted suicide. Paediatric patients, particularly those with other comorbid neurological conditions, may have a higher risk of aspiration following seizures than more healthy patients with epilepsy (Hitiris et al 2007; Tomson et al 2004). It is unclear in these studies whether VNS therapy contributed to aspiration and, ultimately, death.

Further to this, coughing was reported in a considerable proportion of studies of patients receiving VNS therapy. The associated risk of significant aspiration appears very low.

Hoarseness or voice alteration was reported in the majority of patients who received VNS therapy. There appeared to be two forms of hoarseness. The first occurred immediately after implantation of the device. This was often the more severe form and was likely to be caused by manipulation of the vagus nerve during the implantation procedure. In the majority of cases this hoarseness and vocal cord paralysis resolved after several months. The second and milder form of hoarseness was primarily related to stimulation of the vagus nerve. This was a well-tolerated and transient form of hoarseness which generally occurred when stimulation settings were increased.

Pain associated with VNS therapy was generally attributed to stimulation by the device. Some reports were made of pain at the site of implantation but most pain was reported

in the throat and neck. In general, pain was well tolerated and limited to periods of stimulation or following increased stimulation parameters.

The potential for infection exists with any device that is implanted. With VNS, infection was not particularly frequent but could occur either post-operatively or during long-term follow-up, and was the most common cause of device removal in children.

Intraoperative arrhythmia was rarely reported in the included studies. In the two studies in which it was reported, it occurred at a rate of 11% and 1%, respectively (Ardesch et al 2007b; Vonck et al 2004). These incidents did not result in the removal of the VNS device and no further adverse sequelae were reported.

Effectiveness

As in the assessment of the safety of VNS plus AED therapy in children, no comparative studies relative to AED therapy alone, with or without the ketogenic diet, were identified in this assessment of effectiveness.

There were no comparative data identified in regard to a reduction in the occurrence of epilepsy-related deaths (eg SUDEP or status epilepticus). However, the fact that such deaths often occur following, or as a result of, a seizure means that it is likely that epilepsy-related deaths may decrease if seizure frequency is also reduced. Thus, seizure frequency is likely to be an intermediate measure of epilepsy-related death. Annegers et al (2000) reported a crude mortality rate of 7.9 per 1,000 person-years in a cohort of 1,819 patients receiving VNS therapy. This outcome should be considered with some caution as not all patients in the cohort would be considered eligible for VNS therapy, according to the clinical pathway described in this assessment.

Quality of life was reported in a number of studies using both condition-specific and generic quality of life instruments and, in general, did not appear to vary according to VNS impact on seizure frequency. It is possible that the quality-of-life tools were insensitive or the studies were too small to capture statistically significant effects. In six adult studies two reported no change in quality of life in patients with partial epilepsies using generic instruments (Chavel et al 2003; Morrow et al 2000). Another study by McLachlan et al (2003) reported change in quality of life using the condition-specific QOLIE-89 questionnaire, and the ELDQOL for patients with considerable mental disability associated with their epilepsy. A statistically significant improvement in quality of life was seen in 19 patients who completed the QOLIE-89; however, only 23% of these patients reported an improvement in quality of life which was clinically relevant. For the patients with substantial mental disabilities, statistically significant improvement in quality of life was seen only in relation to seizure severity.

In children quality of life was reported in 11 studies using both generic and condition-specific instruments. These studies reported varying results, which may highlight the importance of using condition-specific instruments. In the good-quality study by Parker et al (1999), which used the Wellcome QOL assessment tool designed specifically for populations with Lennox-Gastaut syndrome, improvements were seen only in behaviour and side effects of treatment, and not in regard to other domains such as quality of life, overall health, seizure severity or treatment efficacy. Two studies used visual analogue scales to determine improvement in quality of life (Hallbook et al 2005b; Lundgren et al 1998a). The fair-quality study by Hallbook et al (2005) erred in the reporting of results,

which were not consistent with the described method of assessment of quality of life; attempted communications with the authors were unable to clarify the situation. Lundgren et al (1998) reported a 60% improvement in quality of life at 24 months in 2 of 16 patients; however, at 12 months, using data from all 16 patients, this improvement was considerably more modest at 30%.

Overall, the lack of consistency in reporting, as well as the disparate and non-comparative results, makes it difficult to draw conclusions regarding the effect of VNS plus AED therapy on quality of life. However, clinical experience in Australia suggests that improvements in quality of life can be seen even without noticeable seizure reduction (expert opinion of MSAC Advisory Panel, 2008). Expert opinion also suggests that the instruments used to detect such changes in quality of life may not be capable of doing so in this population of patients. It is suggested that subjective improvements in quality of life are seen via parental reporting (expert opinion of MSAC Advisory Panel, 2008).

Four comparative studies reported on the effectiveness of VNS plus AED therapy compared with AED therapy alone in adults. Three of these studies reported change in seizure frequency following VNS therapy in adult populations with partial epilepsy (Clarke et al 1997; Marrosu et al 2005; Marrosu et al 2003), and the fourth reported the same outcome in a population of patients with either partial or generalised epilepsies (Boon et al 2002). The study of highest quality was a randomised active-controlled trial (level II intervention evidence) of 12 weeks duration which compared high VNS stimulation parameters with low (and presumably of no clinical benefit) stimulation parameters (Clarke et al 1997). In this study AED dosages were maintained at the same level; therefore, any change in seizure frequency could be attributed to VNS therapy. After 12 weeks, seizure reductions of 50% in the group receiving high stimulation, and 8% in the low stimulation group, were seen. Although the study was of a randomised design, the authors have not stated how the randomisation was conducted, nor have they indicated the baseline seizure frequencies of the two groups.

The three further non-randomised, comparative (level III-2 intervention evidence) studies identified reported on change in seizure frequency with VNS plus AED therapy relative to AED therapy alone. AED regimens were kept constant in terms of AED and dosage in one study (Marrosu et al 2005), but in the other two studies drug regimens were adjusted according to the needs of the patient (Boon et al 2002; Marrosu et al 2003). As such, changes in seizure frequency which occurred in the studies by Boon et al (2002) and Marrosu et al (2003) may not necessarily be attributable to VNS stimulation alone, but rather to VNS therapy in addition to AED therapy. These latter two studies reported substantially greater reductions in seizure frequency in patients receiving VNS plus AED therapy compared with those receiving AED therapy alone (41% versus 6%, and 70% versus 32%, respectively). In the study by Marrosu et al (2005), where AED therapy was held constant, change in seizure frequency between VNS plus AED therapy and AED therapy alone was in the opposite direction—greater seizure reduction was seen in the AED therapy group compared with VNS therapy (67% versus 39%, respectively). These disparate results are not necessarily the result of VNS plus static AED therapy being worse than static AED therapy alone. Rather, they are explained by the population selected for the AED-alone group. These patients were not necessarily eligible for VNS implantation but had been admitted to the Epilepsy Centre for readjustment of their AED therapy. Because they had a considerably lower baseline seizure frequency than patients receiving VNS therapy, they may have been less difficult

to treat. The results of this study by Marrosu et al (2005) should therefore be considered with caution.

Additional low-level evidence (level IV) regarding changes in seizure frequency indicated that VNS plus AED therapy may increase seizure frequency in a small number of patients.

In children VNS plus AED therapy reduced the frequency of seizures by 22–84% in up to 68% of patients. The greatest proportion of responders was seen in patients with Lennox-Gastaut syndrome (Frost et al 2001).

Although the average number of seizures may be notably reduced following VNS plus AED therapy, it is possible that the majority of patients may not achieve a clinically relevant outcome. Hence, it is crucial to also consider the proportion of responders following VNS plus AED therapy—the number of patients who achieve at least a 50% reduction in seizure frequency. Reliable comparative evidence in this assessment indicates that less than half (40%) of patients who receive VNS plus AED therapy will achieve a 50% reduction in seizure frequency (Marrosu et al 2003).

Much of the literature proposed that the effectiveness of VNS therapy to reduce seizure frequency improved over time. This has been difficult to ascertain due to the results reported at the end of follow-up being biased by censored data, due to a considerable number of drop-outs during the study. Many of those lost to follow-up were due to a lack of clinical benefit and the subsequent decision to discontinue VNS therapy.

Seizure severity was reported in some low-level studies (level IV intervention evidence). One study in adults reported a statistically significant improvement in seizure severity using a validated questionnaire. However, the authors did not quantify the improvement.

Limited evidence reported the effectiveness of VNS plus AED therapy in reducing the frequency of drop attacks. Drop attacks are particularly debilitating in people with epilepsy due to the potential for serious injury. They are also important due to the precautions necessary to prevent injury from falls (eg helmet wearing or using a wheelchair). VNS plus AED therapy has the potential to alleviate the risk from drop attacks but evidence of this was generally limited to small sample sizes. In one study of 16 adults drop attacks were reduced by 20–50% in 38% of patients. However, this was accompanied by a similar increase in drop attacks in 25% of patients. In addition, one patient (8%) had an increase of more than 75% in drop attacks. This population also had the highest rate of discontinuation.

Two studies reported considerable reductions in drop attacks following VNS therapy in children. Frost et al (2001) reported a statistically significant reduction in attacks of 88% at 6 months. Although there was a notable decline in the number of patients at 6 months, the authors indicated that this was due to the data collection cut-off point and not patient attrition. Similarly, Patwardhan et al (2000) reported an 80% reduction in atonic seizures following 12 months of VNS therapy. These results suggest that VNS therapy may be more effective at reducing the frequency of drop attacks in children than adults.

Comparative data pertaining to changes in hospitalisations were compromised due to the high probability of selection bias. Boon et al (2002) reported a statistically significant reduction in hospital admission days for patients receiving VNS plus AED therapy compared with patients receiving AED therapy alone. Treatment assignment was based

on the medical opinion of a multidisciplinary team after considering clinical and diagnostic findings. It would follow that treatment assignment was based on the opinion that one treatment was likely to offer better outcomes than the other. As reflected by the disparate number of hospital admissions at baseline, these groups are unlikely to reflect a true comparison of VNS plus AED therapy with AED therapy alone.

Change in the number or dose of AEDs was reported in a number of low-level evidence studies. No statistically significant changes in the drug regimens of patients were reported following VNS plus AED therapy. Expert opinion indicates that, if VNS plus AED therapy was successful in reducing the frequency of seizures, it is likely that the number or dose of AEDs required would also be subsequently reduced (expert opinion of MSAC Advisory Panel, 2008).

Continuation of VNS therapy was mostly reliant on perceived clinical benefit. One study with long follow-up (4–9 years) reported continuing VNS plus AED therapy in only 29% of patients, mostly due to a lack of clinical benefit. As less than half of patients are likely to achieve a clinically relevant outcome of 50% or greater seizure reduction, it is possible that VNS plus AED therapy will be discontinued in a large proportion of patients.

The body of evidence included in this assessment was appraised according to the NHMRC guidelines (NHMRC 2007). This appraisal considered: the evidence-base, in particular the number of studies and their methodological quality; the homogeneity of the studies' results; the clinical relevance of the primary outcomes for safety and effectiveness; the generalisability of the evidence to the population with medically refractory epilepsy which is unsuitable for resective surgery; and the applicability of the evidence to the Australian healthcare system. Table 43 presents the results of the appraisal of the evidence considered in this assessment of VNS therapy for epilepsy.

Table 43 Completed body of evidence assessment matrix

Body of evidence / Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence-base			Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	
Consistency			Some inconsistency reflecting genuine uncertainty around clinical question	
Clinical impact			Moderate	
Generalisability	Population(s) studied in body of evidence are the same as the target population			
Applicability		Applicable to Australian healthcare context with few caveats		

Other relevant considerations

Expert opinion

It is expected that only a small number of patients would be suitable for this therapy. As they are refractory to treatment and many have associated neurological comorbidities, the patients in this group are particularly vulnerable. As such, it is imperative that referral for VNS therapy be provided after consultation with a neurologist who specialises in epilepsy. This is to make certain that only those patients who are appropriately indicated will receive VNS therapy. In addition, it will ensure that patients are evaluated for their suitability for other treatments, such as resective surgery, which could provide them with complete seizure relief.

While it is acknowledged that the implantation procedure is not complex, expert opinion recommends that it is performed by a neurosurgeon. This is to ensure that the appropriate care and setting is provided to patients who are likely to be at high risk of complications from the general anaesthetic, as well as being at risk of post-operative status epilepticus.

There are a number of methodological issues which warrant consideration when examining evidence relating to this therapy. The implantation procedure and the awareness of stimulation of the vagus nerve are associated with a strong placebo effect. The use of sham treatment as a control (where a subtherapeutic dose of VNS stimulation is applied) is appropriate when assessing the effectiveness of VNS therapy. Such a study design was employed when trials (E03 and E05) were conducted for approval of VNS therapy by the Food and Drug Administration (FDA) in the United States. The evidence used for FDA approval could not be included in this assessment as these studies did not explicitly include only patients who were not suitable for, or who had previously failed, resective surgery. Indeed, the E05 trial excluded patients who had previously undergone resective surgery. Therefore, the results of these trials are unlikely to be generalisable to the Australian context.

The E03 and E05 trials reported the effectiveness of VNS therapy on partial epilepsy in the short term by randomising patients over the age of 12 years to either high or low stimulation (Handforth et al 1998; Vagus Nerve Stimulation Study Group 1995). Both multicentre studies reported a statistically significant greater reduction of seizures in the high stimulation group compared with the low stimulation group (data not shown (Handforth et al 1998; Vagus Nerve Stimulation Study Group 1995)). The E05 study reported a statistically significant mean seizure frequency reduction from baseline for both high and low stimulation groups, while the E03 study reported this only for the high stimulation group (data not shown). This comparison of high stimulation with low stimulation provided evidence that high stimulation was the more effective at reducing seizure frequencies in patients with partial epilepsies. Interestingly, although the direction of the effect is the same for the E03 and E05 trials as well as the studies included in this assessment, evidence from the latter indicate that VNS is likely to be more effective in the population subgroup selected for this review (ie consistent with Australian clinical practice) than for the patients included in the E03 and E05 trials.

While the trials used for FDA approval assessed the effectiveness of VNS in patients over the age of 12 years, expert opinion suggests that VNS is more effective in children than adults.

There are substantial difficulties with measuring quality-of-life outcomes in the population of interest in this assessment. Validated quality-of-life instruments which are currently available are unlikely to detect an improvement following VNS therapy as many are not specifically validated for epilepsy patients. Clinical experts indicate that a reduction in seizure frequency is likely to be associated with an improvement in quality of life and that the best predictor of such improvement is seizure freedom. Clinical experience also suggests that there may be improvements in quality of life (according to parental reporting) even without an associated improvement in seizure frequency.

Cost of epilepsy

Epilepsy, particularly epilepsy refractory to medical or surgical treatment, results in many direct and indirect costs. The direct costs may include the ongoing costs of medical consultations, AEDs and hospitalisation for seizures. The indirect costs include the psychosocial influence that epilepsy has on schooling, employment and quality of life, as well as the costs to other people, such as family and carers.

The quality of life for people with intractable epilepsy is poorer than for the general population (Berto 2002). There are a broad range of quality-of-life domains that may be affected due to seizures, social stigma, side effects from treatments and self-imposed social withdrawal. The severity of seizures is strongly associated with anxiety about seizures and social avoidance behaviour (Harden et al 2007). The relationship between the frequency of seizures and anxiety is less clear, as it has been reported that adults who experience more frequent partial seizures have lower anxiety than people who experience a lower frequency of seizures (Goldstein & Harden 2000).

School performance is influenced by many variables in children with epilepsy, including the cognitive effects of seizures and the impact of AEDs (Aguiar et al 2007). Children with symptomatic epilepsy (especially medically intractable) often have reduced levels of school attendance due to seizures, medical appointments and overprotective parents, which may further exacerbate academic difficulties (Aguiar et al 2007). This effect is not isolated to the epileptic children themselves, and may also decrease the school attendance of siblings (Aguiar et al 2007).

Uncontrolled epilepsy may also make it difficult to find employment due to objective restrictions, such as inability to drive a vehicle or be in situations where they may be liable to injury (Smeets et al 2007). In addition, stigma and lack of knowledge by employers may also increase job difficulties, through fear and negative attitudes towards epilepsy (Smeets et al 2007).

Access to VNS

Once the VNS device has been inserted, it can only be turned on 10 days after insertion (Royal Children's Hospital Melbourne 2007). Regular appointments with a neurologist in a specialist epilepsy centre are then required for several months. The functioning of the VNS and the frequency of seizures are monitored, and the stimulating parameters of the VNS are increased as tolerated (Royal Children's Hospital Melbourne 2007). This regular follow-up would make access to VNS therapy difficult for patients living in remote areas, and at a substantial cost due to travel requirements or costs of temporary accommodation.

It is important to remember that patients who have a VNS device implanted should not undergo whole body MRI (Cyberonics Inc 2006).

The battery in the VNS unit needs to be replaced once it is depleted. Battery life depends on programmed output current and frequency of stimulation, (between 1 to 16 years). At the end of battery service, the pulse generator is replaced ($18,300), requiring additional surgery which is itself associated with risks and additional costs. Patients receiving a new pulse generator would require a general anaesthetic (expert opinion of MSAC Advisory Panel for Application 1118, 2008).

Adults with intractable epilepsy are less likely to be fully employed and have private health insurance than the general population. For many adults it is therefore expected that, due to financial constraints, they would only be able to receive VNS therapy if it is offered in the public health system.

Determination of suitability

Patients need to receive a comprehensive neurological assessment at an epilepsy centre by a neurologist who specialises in epilepsy to determine suitability for VNS placement. Some epilepsy centres in the United Kingdom and the United States avoid thorough assessment of patients in regard to their suitability for resective surgery, and provide them with VNS therapy without surgical evaluation. In doing this, there is the potential to reduce the effectiveness of VNS therapy by employing it on unsuitable candidates. It should only be used as a potential treatment for patients who are refractory to AEDs, and who have had unsuccessful resective surgery or are unsuitable for such surgery (expert opinion of MSAC Advisory Panel for Application 1118, 2008). The effectiveness of VNS in patients for whom AEDs or resective surgery can successfully manage symptoms has not been evaluated in this assessment.

Lack of alternative treatment options

It is expected that patients who meet the eligibility requirements for VNS therapy would desire to receive it, as the only other option is continued AED therapy (which is ineffective within this population) or palliative surgery. Although the mechanisms of action of VNS on mood are unknown, epilepsy patients with comorbid depression may also desire VNS for its ability to lessen the frequency of seizures and for its reported ability to improve mood (Krishnamoorthy 2003).

What are the economic considerations?

The purpose of economic evaluation is to assist decision-makers in ensuring that society's ultimately scarce resources are allocated to those activities from which we will get the most value. That is, it seeks to enhance economic efficiency. To determine whether further economic evaluation is required, the comparative safety and effectiveness of the intervention must first be determined.

The comparator for VNS therapy plus AED therapy is AED therapy alone in adults, and AED therapy with or without the ketogenic diet in children. No comparative evidence of VNS plus AED therapy relative to AED therapy with or without the ketogenic diet in children was identified. Therefore, it was not possible to determine the comparative safety and effectiveness of these two interventions in children and, consequently, an economic evaluation in this population cannot be conducted.

Comparative evidence regarding the safety of VNS plus AED therapy relative to AED therapy alone was not available in adults; however, there was an indication from low-level non-comparative evidence of some adverse events caused by VNS implantation and stimulation. Therefore, it is logical to assume that adverse events resulting from VNS therapy will be in addition to those which are a consequence of AED therapy, and that VNS plus AED therapy is no safer than AED therapy alone in adults.

Given the decrease in safety with VNS plus AED therapy compared to AED therapy alone, there must be a net benefit in terms of improvement in effectiveness with VNS placement to proceed with a cost-effectiveness or cost-utility analysis (Table 44).

Table 44 Type of economic evaluation that should be presented for various classifications of a service under MSAC consideration

Classification	Type of economic evaluation
The service under MSAC consideration is more effective than the appropriate comparator and is associated with improved safety.	Cost-effectiveness or cost-utility
The service under MSAC consideration is more effective than the appropriate comparator and is no worse than the comparator in terms of safety.	Cost-effectiveness or cost-utility
The service under MSAC consideration is more effective than the appropriate comparator but is associated with reduced safety:	
i) Overall, there are net benefits to patients as the benefits from improved effectiveness outweigh the harms from reduced safety.	Cost-effectiveness or cost-utility
ii) Overall, the service under MSAC consideration is no worse than the comparator because the benefits from improved effectiveness at least offset the harms from reduced safety.	Cost-effectiveness (which may be reducible to cost-comparison—ie presentation of an incremental cost-effectiveness for the base case may be inappropriate if net benefits are assumed to be zero.)
iii) Overall, there are net harms to patients as the harms from reduced safety outweigh the benefits from improved effectiveness.	No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this service.
The service under MSAC consideration is no worse than the comparator in terms of effectiveness but is associated with improved safety.	Cost-effectiveness or cost-utility
The service under MSAC consideration is no worse than the comparator in terms of both effectiveness and safety.	Cost-comparison (however, it may be appropriate to provide cost-effectiveness analyses as sensitivity analyses if there is uncertainty around the conclusion that the service is no worse that the comparator in terms of effectiveness and safety.)
The service under MSAC consideration is no worse than the comparator in terms of effectiveness but is associated with reduced safety.	No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this service.
The service under MSAC consideration is less effective than the comparator but is associated with improved safety:	
i) Overall, there are net benefits to patients as the benefits from improved safety outweigh the harms from reduced effectiveness.	Cost-effectiveness or cost-utility
ii) Overall, the service under MSAC consideration is no worse than the comparator because the benefits from improved safety at least offset the harms from reduced effectiveness.	Cost-effectiveness (which may be reducible to cost-comparison—ie presentation of an incremental cost-effectiveness for the base case may be inappropriate if net benefits are assumed to be zero.)
iii) Overall, there are net harms to patients as the harms from reduced effectiveness outweigh the benefits from improved safety.	No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this service.
The service under MSAC consideration is less effective than the comparator and is no worse than the comparator in terms of safety.	No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this service.
The service under MSAC consideration is both less effective than the comparator and is associated with reduced safety compared with the comparator.	No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this service.

Four comparative studies in adults were identified which provided data regarding the number of patients who achieve at least a 50% reduction in seizure frequency, change in seizure frequency and change in hospital admission days.

These studies suggest that VNS plus AED therapy is more effective than AED therapy alone in reducing seizure frequency and hospital admission days, as well as being able to achieve a higher proportion of patients who obtain a 50% or greater reduction in seizure frequency.

However, the evidence providing this effectiveness data is not strong. Close examination of the comparative evidence indicates that two studies were limited by selection bias in the AED therapy groups, as previously highlighted in the Discussion section of this report (Boon et al 2002; Marrosu et al 2005). The randomised trial by Clarke et al (1997) (level II intervention evidence) provided data regarding the change in seizure frequency following VNS plus AED therapy; however, these data are limited not only by the small sample size (n=10) but also the short-term follow-up of 12 weeks. Marrosu et al (2003) provided level III-2 intervention evidence regarding the comparative reduction in seizure frequency of VNS plus AED therapy and AED therapy alone. This study had an appropriate comparator population of patients who were receiving AED therapy while waiting for VNS implantation. Although a statistically significant difference reduction of seizure frequency was reported, the sample size studied (n=17) was small; thus, it is unclear whether the results are generalisable to a larger population.

Further data are unlikely to become available as a number of studies, with large sample sizes and randomised allocation, have previously been conducted but on a broader patient population. These studies have been excluded from this assessment as they did not meet the stringent inclusion criteria regarding populations which are not suitable for resective surgery or have previously failed resective surgery.

Based on the available evidence included in this assessment, it would be inappropriate to proceed with an economic evaluation. Instead, a financial analysis of the expenditures associated with VNS plus AED therapy in adults and children, relative to AED therapy with or without the ketogenic diet, has been conducted.

As VNS is an adjunct to AED therapy, the costs associated with AED therapy alone will not be considered in this analysis. Therefore, it should be noted that the costs associated with VNS therapy are in addition to those associated with AED therapy. It has been assumed that, because the ketogenic diet is not offered in the private health sector, the comparator for children in the private health sector is AED therapy alone.

Financial incidence analysis

Likely number of procedures in a typical year

No specific data are available to indicate the prevalence of medically refractory epilepsy and the subsequent number of patients who would be eligible for VNS therapy in Australia. The AIHW has reported that approximately 69,700 persons have epilepsy in Australia (Australian Institute of Health and Welfare 2000). In addition, approximately one-third of the population with epilepsy is likely to have uncontrolled seizures despite multiple trials with different AEDs or polytherapy (Kwan & Brodie 2000). Those people with medically refractory epilepsy would be evaluated for their suitability for resective surgery, and it is estimated that only 1% of the epilepsy population would be considered to be suitable candidates for resection (expert opinion of MSAC Advisory Panel for Application 1118, 2008). Informed opinion has also indicated that approximately 30

devices would be implanted in Australia annually, of which it is likely that eight devices would be implanted in children. Potential leakage in the public sector may increase the number of annual implantations to 75 (MSAC Application 1118, 2007).

Unit costs of the procedure and comparators

In considering the implantation workup for VNS plus AED therapy or AED therapy alone with or without the ketogenic diet, it is assumed that all patients will have previously undergone evaluation for their suitability to resective surgery. Hence, for patients who go on to VNS plus AED therapy or AED therapy alone (with or without the ketogenic diet), the costs associated with pre-surgical evaluation have not been considered here.

Prior to implantation of the VNS device, patients will have one consultation each with the neurologist and the surgeon (Table 45). This analysis may overestimate the consultative fees surrounding the implantation procedure as it assumes that a neurosurgeon will perform the procedure.

Unit costs of VNS implantation involve the professional fee of the surgeon and their assistant, anaesthesia, hospital stay and also the VNS device. Intraoperative testing of the device is conducted by trained specialist staff from the device distributor and is inclusive in the cost of the device.

Before initiating the ketogenic diet, a number of diagnostic tests are performed to assess the metabolic state of the child (

Table 46). Although it has been assumed that the ketogenic diet is only offered in the public healthcare system, the MBS scheduled fee for some items has been used to estimate the costs of these items in the public healthcare sector.

Implementation of the ketogenic diet is offered in centres in Brisbane, Sydney, Melbourne, Adelaide and Perth. The protocol used to initiate the diet is expected to differ between each centre, depending on the baseline and monitoring tests used and the length of hospital stay. It should be noted that initiation of the diet requires a team approach between the neurologist, specialist dietician and epilepsy nurse (Neurology Department of the Royal Children's Hospital Melbourne 2008).

In this analysis it has been assumed that the ketogenic diet is initiated in a public hospital facility and requires a 4-day stay (

Table 46). The patient would be under the supervision of an epilepsy nurse, a specialist dietician experienced with the diet and a paediatric neurologist. Upon admission, baseline tests would be performed, including blood glucose and fasting lipids, electrocardiogram (ECG) and echocardiogram. During the patient's stay, blood glucose and ketones, as well as urinary ketone levels, would be monitored. Ketone levels are monitored using dipsticks and would therefore be covered under pathology costs incorporated into the total charge per AR-DRG. Costs associated with the time of the specialist dietician and epilepsy nurse are based on estimates made in 2003, and are likely to underestimate the current costs (Neurology Department of the Royal Children's Hospital Melbourne 2008). It has been assumed that the epilepsy nurse and dietician would spend 5 and 15 hours, respectively, with the patient during their stay.

In summary, the total cost of implanting the VNS device is $21,733 in adults and children. This includes the cost of the device and hospital stay, which would be incurred by the private patient. These costs are reflective of a private patient in a private hospital facility for surgical procedures. The total cost of initiating the ketogenic diet is $3,786, which also includes the cost of the hospital stay, professional services and metabolic tests. These costs are indicative of the costs incurred by a private patient in a private hospital, and assume that costs incurred in the public hospital system are reflective of those in private hospitals.

Table 45 Procedural costs associated with VNS therapy in adults and children

Item	Source of estimate	Schedule fee ($)
Pre-procedural costs		
Pre-implantation consult with neurologist	MBS item 110	136
Pre-implantation consult with surgeon	MBS item 6007	117
Procedural costs		
Professional fee	MBS item 39138	609
Surgical assistance	MBS item 51303	122
Pre-anaesthetic consult	MBS item 17610	39
Anaesthesia initiation	MBS item 20320	107
Anaesthesia time units[a]	MBS item 23083	143
VNS implant device	Expert opinion of Advisory Panel	18,300
Hospital facility costs—overnight stay	Average total charge per AR-DRG version 5.1 Private Hospitals Data Bureau B07B Prphl & Cranl Nerv & Oth PR-CC ALOS 1.0 days	1,848
Post-procedural costs		
4 consults[b] with neurologist for adjustments following implantation	MBS item 116	273
Post-implantation consult with surgeon	MBS item 6009	39
Total		21,733

MBS = Medicare Benefits Schedule (Department of Health and Ageing 2007a); ALOS = average length of stay; AR-DRG = Australian Refined – Diagnosis Related Groups; [a] use of a modifier for age for anaesthesia would only be applicable for patients aged <1 year or >70 years. VNS therapy is not used in patients <1 year of age. The proportion of patients >70 years of age likely to receive VNS therapy was considered trivial for the purposes of this financial estimation; [b] expert opinion of Advisory Panel

Table 46 Procedural costs associated with the ketogenic diet in children

Item	Source of estimate	Schedule fee ($)
Pre-procedural costs		
Initial consultation with paediatric neurologist	MBS item 110,116	205
FBC	MBS item 65070	17
UEC, LFT, blood glucose, lipids	MBS item 66515	20
Procedural costs		
Dietician	RCH Melbourne Childhood epilepsy program 2003 estimate	488
Epilepsy nurse specialist	RCH Melbourne Childhood epilepsy program 2003 estimate	165
Paediatric neurologist	MBS item 116	205
Baseline blood tests, fasting lipids and blood sugar	MBS item 66503	12
Monitoring of blood glucose	MBS item 66500	156
ECG	MBS item 11700	28
Echocardiogram	MBS item 55113	231
Hospital stay / facility fee	Average total charge per AR-DRG Round 9 (2004–05) National Hospital Data Collection v5.0 (Public Sector) B76B Seizure - Cscc ALOS 1.92 days	1,919
Post-procedural costs		
Follow-up consultations with paediatric neurologist—6 per year	MBS item 116	341
Total		3,786

FBC = full blood count; UEC = urea, electrolytes, creatinine; LFT = liver function tests; RCH = Royal Children's Hospital; MBS = Medicare benefits schedule (Department of Health and Ageing 2007a); ALOS = average length of stay; AR-DRG = Australian Refined – Diagnosis Related Groups; ECG = electrocardiogram

Costs to the Medicare Benefits Scheme (MBS)

The Australian Government will be responsible for payment of the rebate on items from the Medicare Benefits Schedule. As the implantation of the VNS device will be performed in a hospital facility, the rebate will be 75% of the scheduled fee for a private patient in a private hospital facility.

A comparison of MBS item payments, including pre- and post-procedural costs associated with VNS therapy, is provided in Table 47.

Table 47 Costs of MBS item numbers associated with VNS therapy

MBS item	VNS therapy
Pre-procedure	
Pre-implantation consult with neurologist	$136
Pre-implantation consult with surgeon	$117
Procedure/therapy	
Professional fees	$609
Surgical assistance	$122
Pre-anaesthetic consult	$39
Anaesthesia initiation	$107
Anaesthesia time units	$143
Post-procedure/therapy	
4 consults with neurologist for adjustments following implantation	$273
Post-implantation consult with surgeon	$39
Total	**$1,585**

Expert opinion suggests that most patients with epilepsy as severe as those with medically refractory epilepsy who are unsuitable candidates for resective surgery, or have previously failed such surgery, would not have private health insurance. As such, the majority of patients would be treated in the public healthcare system. A reasonable public to private patient split for such a population is recommended as 85% and 15% for adults and 95% and 5% for children (expert opinion of MSAC Advisory Panel, 2008). Based on this assumption, there are likely to be three adults who receive VNS in the private sector annually and one child every 2–3 years. However, for the purposes of this assessment, it will be assumed that one child per year receives VNS therapy in the private healthcare system. As it is estimated that there will be approximately 30 procedures performed annually, of which 26 would occur in the public sector, approximately 4 patients would receive VNS therapy in the private sector and subsequently be eligible for MBS reimbursement.

Assuming that 15% of children attempt the ketogenic diet, of the remaining seven children receiving VNS therapy in the public sector, one would attempt the diet. However, as the ketogenic diet is not offered in the private healthcare sector, the incremental costs of VNS plus AED therapy over the ketogenic diet have not been calculated.

The financial implications of subsidising VNS therapy over and above AED therapy are calculated by multiplying the estimated cost per procedure by the expected uptake of the procedure in private hospitals. Assuming four patients (including children) would receive VNS therapy in a private hospital annually, the total initial annual cost of VNS therapy in addition to AED therapy would be $6,341. Downstream costs such as device replacement and the potential surgical risks involved have not been considered in this analysis.

Costs to the states and territories

Under the current Australian Healthcare Agreements, the states and territories fund inpatient procedures on public patients in public hospitals, as well as public patients in an

outpatient facility. To estimate the costs to the states and territories, three assumptions have been made—that the unit costs of the procedure are the same for a public patient as they are for a private patient; that 26 patients (19 adults and 7 children) would receive VNS therapy in addition to AED therapy; and that 15% of eligible children would attempt the ketogenic diet. As indicated in Table 48, the costs of providing VNS therapy are $412,927. The total cost of initiating the ketogenic diet in one child is $3,786. These costs are in addition to those of AED therapy.

Table 48 Total costs to the states and territories

	VNS therapy	Ketogenic diet
Cost of procedure/therapy	$21,733	$3,786
Number of procedures/therapy	19	1
Total cost	$412,927	$3,786

Total healthcare costs

Total healthcare costs incorporate all direct costs associated with providing VNS therapy, regardless of the person or agency who incurs them.

The total healthcare costs associated with the implementation of VNS therapy in 30 patients would be $652,000. This cost is in addition to the costs of AED therapy. The total healthcare costs for the equivalent comparator therapy would be $3,786 in addition to the costs of AED therapy. The additional comparator costs to AED therapy are those of children who proceed with the ketogenic diet. Therefore, if the introduction of VNS plus AED therapy in children would replace the use of the ketogenic diet or AED therapy alone, the incremental healthcare costs would be approximately $648,200.

As indicated previously, there is potential for leakage to occur in the utilisation of VNS therapy in the public health sector (expert opinion of MSAC Advisory Panel, 2008). This could see the number of patients initiating VNS therapy increase to 75 annually. The total healthcare costs would increase to $1,630,000 if the potential for leakage in the public sector was realised (Table 49). Again, these costs are in addition to those of AED therapy alone. If VNS therapy were to be initiated in 75 patients annually, then it would likely replace the use of the ketogenic diet in three children. As such, the incremental healthcare costs of VNS therapy would be approximately $1,618,000 annually.

Table 49 Sensitivity analysis on the utilisation of VNS therapy

Cost of implementing VNS therapy (per patient)	Utilisation	Total healthcare costs
$21,733	30	$652,000
	75	$1,630,000

These estimates are likely to under-represent the costs for VNS therapy as they do not include the costs of removing and replacing pulse generators once the battery is depleted. It should also be noted that any downstream cost savings due to a reduction in AED dose or hospitalisations is uncertain given the limited and equivocal comparative data that are available.

Discussion of economic considerations

Although a cost-effectiveness analysis of VNS therapy in addition to AED therapy is warranted, lack of available and appropriate data and, more importantly, uncertainty regarding the net benefit of VNS therapy have prevented this being conducted.

A financial analysis of the intervention and its comparator has been conducted to indicate the expenditures involved with each therapy from a healthcare system perspective, excluding downstream costs associated with pulse generator replacement after battery depletion.

Based on the assumption of 30 patients receiving VNS therapy in addition to AED therapy, of which 26 would do so in the public sector, the **total** cost of VNS therapy to the whole health system (MBS and states and territories) is an additional $419,000 annually to the cost of AED therapy. Potential leakage in the public health sector is likely to increase this estimate to $1,630,000. After incorporation of the costs of the ketogenic diet comparator, the incremental cost to the whole health system is $416,000 for the base case and $1,618,000 for the sensitivity analysis.

As the ketogenic diet is only offered in the public healthcare system, the financial implications to the MBS alone are those associated with VNS therapy and not the ketogenic diet comparator. As such, the cost per patient eligible for MBS reimbursement for VNS therapy is in the order of $1,600 annually (total of $6,341 for the expected uptake).

The states and territories alone will bear the costs (including that of the devices) for the majority of patients who receive VNS therapy. For 26 patients they are likely to incur expenditure in the order of $413,000 annually for providing VNS therapy. The comparator in children is expected to require an expenditure of $3,800 annually, which means there would be an incremental cost of $409,200.

The financial impact of VNS therapy in terms of total healthcare costs is in the order of $650,000 annually for provision to 30 patients.

When considering the expected uptake of the therapy, and the likely public–private split of patients, the impact on the Australian healthcare system is expected to be not insignificant relative to the comparator therapy.

The uncertainty regarding net benefits from this therapy, potential downstream costs associated with safety risks, and known downstream costs associated with the need for surgery for pulse generator replacement after battery depletion (approximately $18,000) means that it is unclear whether VNS therapy provides value for money in this patient population.

Conclusions

Safety

This assessment reviewed the published evidence regarding the comparative safety of VNS plus AED therapy relative to AED therapy alone in adults, and AED therapy with or without the ketogenic diet in children. The populations considered were strictly those patients with medically refractory epilepsy who had previously failed resective surgery or for whom such surgery was not considered an option.

Complications associated with implantation included infection and vocal cord paralysis due to manipulation of the vagus nerve. In adults these events occurred in up to 20% and 11%, respectively; and in children the incidence of infection occurred in up to 11% of patients studied. The most common outcome of infection in children was removal of the VNS device, with 55% of infections requiring device removal.

Voice alteration and coughing were the most commonly reported adverse events associated with VNS stimulation. Voice alteration or hoarseness was reported by the majority of adults and children receiving VNS therapy, but more commonly in adults than children (12–100% and 8–53%, respectively). Voice alteration was, in general, transient or was resolved with a reduction in stimulation parameters.

Death was reported following VNS therapy in two patients although these were not clearly attributable to VNS. People with uncontrolled epilepsy are at higher risk of death than the general population. This is related either directly or indirectly to the occurrence of seizures; thus, a lack of effectiveness of VNS in preventing seizures could potentially impact on epilepsy-related death.

Other complications reported included stimulation pain, paraesthesia, dyspnoea upon physical exertion, anorexia and, rarely, intraoperative arrhythmia.

VNS therapy itself appears to be an acceptably safe procedure in terms of implantation surgery and delivery of stimulation. It is important to keep in mind that VNS therapy will be concomitant with AED therapy, which itself may be associated with adverse side effects. As such, any complications associated with VNS therapy will be in addition to AED therapy. It follows, therefore, that VNS plus AED therapy is no safer than AED therapy alone in patients (adults or children) with medically refractory epilepsy.

Effectiveness

No evidence was identified to assess the comparative effectiveness of VNS plus AED therapy versus AED therapy alone in children.

There does not appear to be a large difference between the effectiveness of VNS plus AED therapy in partial or generalised epilepsies. Any difference, if it existed, would be difficult to detect due to the variation in seizure frequency response.

Based on level II and level III-2 intervention evidence, of fair to good quality although small sample size, it would appear that VNS plus AED therapy was more effective in

reducing the average seizure frequency in adults than AED therapy alone (41–50% and 6–8%, respectively). However, this statement comes with the stipulation that a clinically relevant reduction in seizure frequency would be seen in less than half (40%) of the adults who receive this therapy. Low-level evidence suggests that VNS plus AED therapy has a clinically significant effect in reducing seizure frequency in children with Lennox-Gastaut syndrome.

In both adults and children, no comparative evidence was available to determine whether VNS plus AED therapy reduced the epilepsy-related mortality of patients, nor was there strong evidence of an improvement in quality of life. Improvements which were seen appeared to be small and limited. Reports of changes to the AED regimen were inconclusive and no statistically significant change to the AED regimen following VNS plus AED therapy was reported.

One study of level III-2 intervention evidence provided results showing a comparative decrease in hospital admission days; however, the study was highly likely to have been affected by selection bias and the results should not be considered trustworthy.

There is no strong evidence to indicate that seizure severity is improved in either adults or children. One low-level study (level IV intervention evidence) reported a statistically significant improvement in adults, although the degree of improvement was not quantified.

VNS effectiveness at reducing drop attacks is likely to be greater in children than in adults. Two studies (level IV intervention evidence) reported at least an 80% reduction in drop attacks in children, and one study of adults reported a 20–50% reduction in less than half (38%) of patients.

The continuation rate of VNS plus AED therapy ranged from 29% to 100%. Continuation was closely associated with the effectiveness of VNS stimulation and AED therapy to provide a clinically relevant benefit in terms of reducing seizure frequency and/or severity.

For a small proportion of patients, VNS plus AED therapy is able to provide complete freedom from seizures; however, overall, this therapy is likely to provide a clinically relevant benefit to less than half of the patients for whom it is suitable.

Economic considerations

The improved effectiveness of implantation of VNS therapy plus AED therapy compared to AED therapy alone suggests that the cost-effectiveness of VNS plus AED therapy against the comparators should be investigated. However, a lack of data and uncertainty regarding net benefit resulted in no formal economic evaluation being conducted; instead, a financial analysis of the expenditures associated with the therapies was performed.

The expected uptake of this procedure (estimated at 30 procedures annually) is relatively small and therefore is not expected to result in a significant financial burden to the Australian Government.

The greatest cost associated with this therapy is the cost of the device itself. Unless performed in the public sector, this cost would be borne by the patient. In addition, at the end of battery life a new device is required to be implanted, which will increase the costs of delivering this therapy in the long term. The costs of implanting a new device have not been considered in this assessment.

It is estimated that four patients would receive VNS therapy in the private sector annually; this will incur an initial annual cost to the Australian Government of $6,341 relative to AED therapy.

Total cost to the Australian healthcare system for VNS therapy is estimated to be $416,000 annually.

The financial implications of all healthcare costs associated with the implementation of VNS therapy for 30 patients is in the order of $650,000 in addition to the costs of AED therapy and excluding likely significant downstream costs.

The potential for leakage in the public sector would be expected to increase the utilisation to 75 patients annually and the subsequent healthcare costs to $1,630,000 per year.

Recommendation

The MSAC has considered the safety, effectiveness and cost-effectiveness for vagus nerve stimulation in addition to anti-epileptic medication for patients with medically refractory epilepsy. It was compared with continued or modified anti-epileptic drug therapy for all patients, and for children it was also compared with or without a ketogenic diet.

MSAC finds the procedure is reasonably safe in the context of the condition being treated.

MSAC finds there is insufficient evidence of effectiveness and net benefit of vagal nerve stimulation therapy for patients with medically refractory epilepsy.

Formal economic analysis was not conducted in view of the uncertainty of net clinical benefit.

MSAC recommends that public funding arrangements for vagus nerve stimulation for epilepsy remain unchanged.

The Minister for Health and Ageing noted this advice on 28 August, 2008.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or affiliation
Dr Stephen Blamey (Chair)	General surgery
Professor Brendon Kearney (Deputy Chair)	Health administration and planning
Dr William Glasson (Second Deputy Chair)	Ophthalmology
Associate Professor John Atherton	Cardiology
Associate Professor Michael Cleary	Emergency medicine
Associate Professor Paul Craft	Clinical epidemiology and oncology
Professor Geoff Farrell	Gastroenterology
Dr Kwun Fong	Thoracic medicine
Professor Richard Fox	Oncology
Professor Jane Hall	Health economics
Professor John Horvath	Department of Health and Ageing Chief Medical Officer
Associate Professor Terri Jackson	Health economics
Associate Professor Frederick Khafagi	Nuclear medicine
Dr Ray Kirk	Health research
Dr Ewa Piejko	General practice
Dr Ian Prosser	Haematology

Ms Sheila Rimmer	Consumer health issues
Dr Judy Soper	Radiology
Professor Ken Thomson	Radiology
Dr David Wood	Orthopaedics
Mr Peter Woodley	Department of Health and Ageing representative

Appendix B Advisory panel and Evaluators

Advisory panel application 1118 - VNS for epilepsy

Advisory panel	
Dr Ewa Piejko (Chair)	Member of MSAC General practice
Dr Stephen Blamey	Chair of MSAC Surgeon
Professor Samuel Berkovic	Co-opted expert Neurologist
Ms Margaret Charlton	Consumer Health Forum nominee
Professor Andrew H Kaye	Co-opted expert Neurosurgeon
Dr Lakshmi Nagarajan	Australian and New Zealand Association of Neurologists (ANZAN) nominee Paediatric neurologist
Evaluators	
Ms Liz Buckley, Research Officer Ms Tracy Merlin, Manager Professor Janet Hiller, Director	Adelaide Health Technology Assessment (AHTA)

Appendix C Search strategies

Table 50 Search terms used to identify relevant studies regarding VNS therapy

Area of inquiry	Search terms
Safety, effectiveness of VNS	epilepsy [MeSH] OR epilep* OR seizures [MeSH] OR seizure* OR convuls*) AND ((refractory OR intractable OR drug-resistance [MeSH] OR resist*) OR (anticonvulsants/adverse effects [MeSH] OR ((drug OR therap* OR pharmaceutical* AND ((adverse AND (effect* OR event*) OR harm* OR toxic*)) AND ((vagus nerve[MeSH] OR vag* nerve[Text]) AND stimulat*) OR VNS OR (electrical stimulat*) OR (vagus nerve stimulat*) OR neurostimulation OR (electric stimulation therapy [MeSH]) OR " NCP" OR " NeuroCybernetic Prosthesis" [Text]

Table 51 Bibliographic databases used to identify literature on the safety and effectiveness of VNS therapy

Electronic database	Time period
CINAHL	1990 – 10/07
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	1990 – 10/07
Current Contents	1998 – 10/07
Embase.com (including Embase and Medline)	1990 – 10/07
Pre-Medline	1990 – 10/07
ProceedingsFirst	1993 – 10/07
Web of Science – Science Citation Index Expanded	1990 – 10/07
EconLit	1990 – 10/07

Table 52 Other sources of literature

Source	Location
Internet	
NHMRC – National Health and Medical Research Council (Australia)	http://www.health.gov.au/nhmrc/
US Department of Health and Human Services (reports and publications)	http://www.os.dhhs.gov/
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/greylit/index.shtml
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
U.K. National Research Register	http://www.update-software.com/National/
Google Scholar	http://scholar.google.com/
Hand searching (journals from 2006–2007)	

Acta neurochirurgica	Library or electronic access
Acta neurochirurgica. Supplement	Library or electronic access
Epilepsia	Library or electronic access
Epilepsy & behaviour	Library or electronic access
Epilepsy research	Library or electronic access
Journal of clinical neurophysiology	Library or electronic access
Neurology	Library or electronic access
Seizure	Library or electronic access
Expert clinicians	
Studies other than those found in regular searches	MSAC Advisory Panel
Pearling	
All included articles had their reference lists searched for additional relevant source material	

Table 53 Specialty websites

Organisation	Website location
Epilepsy Action Australia	www.epilepsy.org.au
Neurosurgical Society of Australasia	www.ns-aus.affiniscape.com
Epilepsy.com	www.epilepsy.com
Epilepsy Foundation of USA	www.epilepsyfoundation.org
Epilepsy Research UK	www.erf.org.uk
Epilepsy Foundation of Victoria	www.epinet.org.au
The Epilepsy Association of South Australia and Northern Territory Inc	www.epilepsyassociation.com.au
Epilepsy Queensland Inc	www.epilepsyqueensland.com.au
American Epilepsy Society	www.aesnet.org
National Institute of Neurological Disorders/epilepsy	www.ninds.nih.gov/disorders/epilepsy/epilepsy
Children's Epilepsy Program	www.rch.org.au/cep/index.cfm?doc_id=2083
European Epilepsy Academy	www.epilepsy-academy.org/homepage/de/1.html
Epilepsy Ontario	www.epilepsyontario.org
European Federation of Neurological Societies	www.efns.org/index.php

Table 54 Health Technology Assessment Agency websites

AUSTRALIA	
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/open/asernip-s.htm
Centre for Clinical Effectiveness, Monash University	http://www.med.monash.edu.au/healthservices/cce/evidence/
Centre for Health Economics, Monash University	http://chpe.buseco.monash.edu.au
AUSTRIA	
Institute of Technology Assessment / HTA unit	http://www.oeaw.ac.at/ita/e1-3.htm
CANADA	
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)	http://www.aetmis.gouv.qc.ca/en/
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/publications.html
The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/
Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database	http://www.mycabot.ca
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca
Health Utilities Index (HUI)	http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca
DENMARK	
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	www.sst.dk/Planlaegning_og_behandling/Medicinsk_teknologivurdering.aspx?lang=en
Danish Institute for Health Services Research (DSI)	http://www.dsi.dk/engelsk.html
FINLAND	
Finnish Office for Health Technology Assessment (FINOHTA)	http://www.stakes.fi/finohta/e/
FRANCE	
L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)	http://www.anaes.fr/
GERMANY	
German Institute for Medical Documentation and Information (DIMDI) / HTA	http://www.dimdi.de/static/en
THE NETHERLANDS	
Health Council of the Netherlands Gezondheidsraad	http://www.gr.nl/index.php
Institute for Medical Technology Assessment (Netherlands)	http://www.imta.nl/
NEW ZEALAND	
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz/
NORWAY	
Norwegian Centre for Health Technology Assessment (SMM)	http://www.oslo.sintef.no/smm/Publications/Engsmdrag/FramesetPublications.htm
SPAIN	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS)	http://www.isciii.es/htdocs/en/investigacion/Agencia_queES.jsp
Andalusian Agency for Health Technology Assessment (Spain)	http://www.juntadeandalucia.es/salud/orgdep/AETSA/default.asp?V=EN
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.aatm.es/cgi-bin/frame.pl/ang/pu.html
SWEDEN	

Center for Medical Health Technology Assessment	http://www.cmt.liu.se/English/Engstartsida.html
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/www/index.asp
SWITZERLAND	
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
UNITED KINGDOM	
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)	http://www.hta.nhsweb.nhs.uk/
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/index.htm
The European Information Network on New and Changing Health Technologies	http://www.euroscan.bham.ac.uk/
University of York NHS Centre for Reviews and Dissemination (NHS CRD)	http://www.york.ac.uk/inst/crd/
UNITED STATES	
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health – Cost-Utility Analysis Registry	http://www.tufts-nemc.org/cearegistry/index.html
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/htac/index.htm
National Information Centre of Health Services Research and Health Care Technology (US)	http://www.nlm.nih.gov/hsrph.html
Oregon Health Resources Commission (US)	http://egov.oregon.gov/DAS/OHPPR/HRC/about_us.shtml
Office of Health Technology Assessment Archive (US)	http://www.wws.princeton.edu/~ota
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)	http://www.bcbs.com/consumertec/index.html
Veteran's Affairs Research and Development Technology Assessment Program (US)	http://www.va.gov/resdev

Appendix D Studies included in the review

Study profiles of included studies on safety and effectiveness

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
(Alexopoulos et al 2006) Cleveland Clinic, Ohio, USA	Level IV Quality assessment: Poor	Retrospective case series	46 paediatric patients with medically refractory epilepsy who had failed previous resective surgery or were not suitable candidates Median age = 12 years (range 2–18) Male:female = 25:21 ≤12 years: n =21 >12 years: n=25	VNS therapy plus AED therapy VNS settings: Output current ≤ 2 mA On time = 30 seconds Off time = 5 minutes Pulse width = 250 μs Frequency = 30 Hz	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • number of patients with ≥50% or ≥75% seizure reduction • change in AED usage following VNS therapy • functionality of device	Median = 2 years
(Alsaadi et al 2001) University of California, California, USA	Level IV Quality assessment: Good	Retrospective case series	10 adult patients with bilateral independent temporal lobe epilepsy. Patients were medically refractory and had failed intracranial surgery or were not considered suitable candidates Mean age = 38±13 years	VNS therapy plus AED therapy	*Inclusion* Bilateral independent temporal lobe epilepsy *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • number of patients with ≥50% or ≥75% seizure reduction • change in AED usage following VNS therapy	12 months
(Amar et al 2004) USA	Level IV Quality assessment: Fair	Registry study	4,743 patients from the VNS patient registry who had been implanted with the VNS device *Intervention – cranial surgery* (n=921) Median age = 28 years (range 1–66) Male = 55%	*Note: Non-cranial surgery, as a comparator, will not be reported in this assessment*	*Inclusion* Not stated *Exclusion* Not stated	Effectiveness: • change in seizure frequency • number of patients with ≥50% or ≥75% seizure reduction	Up to 24 months

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
			Female = 45% Epilepsy type: Localised = 75% Generalised = 22% Other = 3% *Comparator – no cranial surgery* (n=3,822) Median age = 26 years (range 0–79) Male = 52% Female = 49% Epilepsy type: Localised = 57% Generalised = 40% Other = 3%				
(Andriola & Vitale 2001) State University of New York, USA	Level IV Quality assessment: Poor	Retrospective case series	21 patients with developmental disability or mental retardation. Patients had medically refractive epilepsy and were not suitable candidates for resective surgery Age range = 3–56 years Male:female = 18:3 Epilepsy seizure type: Partial = 13 Generalised = 8	VNS therapy plus AED therapy	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • quality of life	Range = 3 months to >6 years
(Ardesch et al 2007b) Medische Spectrum Twente Hospital, Enschede, Sweden	Level IV Quality assessment: Fair	Case series	19 patients with medically refractory partial epilepsy who were not suitable candidates for resective surgery	VNS therapy plus AED therapy Mean VNS settings: Output current = 1.5 mA On time = 30 seconds Off time = 3 minutes Pulse width =	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • change in AED usage • functionality of device	Mean = 4 years (range 2–6)

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
				250 ms Frequency = 30 Hz			
(Arthur et al 2007) Children's Hospital and Regional Medical Center, Washington, USA *Majority of patients are also reported in Saneto et al (2006)*	Level IV Quality assessment: Fair	Retrospective case series	5 children with definite mitochondrial disease according to modified Walker criteria (Bernier et al 2002) Median age = 6 years (range 4–8.5)	VNS therapy plus AED therapy VNS settings: Output current = 1.25–2.0 mA On time = 30 seconds Off time = 1.1 or 3 minutes Pulse width = 250 or 500 μs Frequency = 30 Hz	*Inclusion* Not stated *Exclusion* Not stated	Effectiveness: • >50% decrease in seizure frequency	Range = 12–48 months
(Ben-Menachem et al 1999) Sahlgrenska University Hospital, Goteborg, Sweden	Level IV Quality assessment: Fair	Prospective case series	64 patients with medically refractory epilepsy who had failed resective surgery or were not suitable candidates for resective surgery Epilepsy seizure/syndrome: PE = 47 Primary generalised seizures = 9 Lennox-Gastaut syndrome = 8	VNS therapy plus AED therapy Output current = 0.25–2.0 mA	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • >50% decrease in seizure frequency • change in seizure frequency following VNS therapy • injuries	Mean = 20 months (range 3–64)
(Blount et al 2006) Children's Hospital Birmingham, Alabama, USA	Level IV Quality assessment: Poor	Retrospective case series	7 patients with medically refractory, multifocal, catastrophic epilepsy Mean age = 1.9±1.2 years Male:female = 4:3	VNS therapy	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • functionality of device	Mean = 21±20 months
(Boon et al 2001b)	Level IV Quality assessment: Fair	Prospective case series	35 patients with partial seizures or Lennox-Gastaut syndrome, who were refractory to AEDs and unsuitable candidates for	VNS therapy plus AED therapy VNS settings:	*Inclusion* Not stated *Exclusion*	Safety: • adverse events during follow-up Effectiveness:	Mean = 35 months (range 9–73)

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
University Hospital, Gent, Belgium *Overlap of patients with Boon et al (2002)*			resective surgery Mean age = 30 years (range 10–49) Male:female = 18:17 Mean AEDs = 3±0.9 (range 1–4)	Output current = up to 3 mA On time = 30 seconds Off time = 300–600 seconds Pulse width = 500 µs Frequency = 30 Hz	Not stated	• change in seizure frequency following VNS therapy • number of patients with ≥50% or ≥75% reduction in seizure frequency	
(Boon et al 2002) Ghent University Hospital, Belgium *Overlap of patients with Boon et al (2001)*	Level III-2 Quality assessment: Fair	Non-randomised comparative study	84 consecutive patients with both PE and generalised epilepsies. Patients underwent pre-surgical evaluation and were assigned to appropriate treatment group by multidisciplinary team Mean age = 32 years (range 5–71 years) *Intervention – VNS therapy* (n=25) *Comparator – continuing AED therapy* (n=25) *Comparator – resective surgery* (n=35)	VNS therapy plus AED therapy *Comparator* • continuing AED therapy • resective surgery *Note: Resective surgery, as a comparator, will not be reported in this assessment*	*Inclusion* Medically refractory epilepsy *Exclusion* Not stated	Effectiveness: • change in seizure frequency following VNS therapy • number of patients with ≥50% or ≥75% reduction in seizure frequency • hospitalisations	Mean = 26 months (range 12–57)
(Brazdil et al 2001) St Anne's Hospital, Brno, Czech Republic	Level IV Quality assessment: Poor	Prospective case series	12 adult patients with medically refractory focal or multifocal epilepsy. Patients had been assessed and found to be unsuitable candidates for resective surgery Mean age = 32.7 years (range 21–53) Male:female = 9:1	VNS therapy plus AED therapy VNS settings: Output current = 0.5–1.0 mA On time = 30 seconds Off time = 5 minutes Pulse width = 500 µs	*Inclusion* Not stated *Exclusion* Not stated	Effectiveness: • change in seizure frequency following VNS therapy • number of patients with ≥50% or ≥75% reduction in seizure frequency	6 months

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
				Frequency = 30 Hz			
(Buoni et al 2004a) Siena, Italy	Level IV Quality assessment: Poor	Case series (unclear if retrospective or prospective)	13 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 17 years (range 6–28) Male:female = 6:7	VNS therapy plus AED therapy VNS settings: Output current = 2.0–2.25 mA On time = 30 seconds Off time = 1 minute 8 seconds – 5 minutes	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy (unreliable data) • quality of life • number of patients with ≥ 50% or ≥ 75% reduction in seizure frequency (unreliable data)	Mean = 22 months (range 8–36)
(Casazza et al 2006) Milano, Italy	Level IV Quality assessment: Fair	Prospective case series	17 adult patients with medically retractable epilepsy who had previously failed resective surgery or were not suitable candidates. Mean age = 34 years (range 21–52) Male:female = 11:6 Epilepsy type/syndrome: Partial epilepsy = 13 Lennox-Gastaut syndrome = 4	VNS therapy plus AED therapy VNS settings: Output current = 0.75–3.0 mA On time = 30 seconds Off time = 5 minutes Pulse width = 500 µs Frequency = 30 Hz	*Inclusion* Not stated *Exclusion* • progressive neurological disorders • evolutive brain lesions • known gastric or cardiac illness	Safety: • adverse events during follow-up Effectiveness: • number of patients with ≥50% or ≥75% reduction in seizure frequency • drop attacks	Range = 4–9 years
(Chayasirisobhon et al 2003) Comprehensive Epilepsy Program, Southern California Permanente Medical Group, California, USA	Level IV Quality assessment: Fair	Case series (unclear if retrospective or prospective)	34 patients with medically refractory epilepsy who were unsuitable for resective surgery. Mean age = 27.6 years (range 5–70) Male:female = 20:14	VNS therapy plus AED therapy VNS settings: Output current = 0.5–3.5 mA On time = 30 seconds Off time = 5 minutes Pulse width =	*Inclusion* • refractory response to AEDs given alone or in combination • at least 6 seizures per month recorded in seizure diaries • unsuitable for	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • quality of life	6 months

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
				500 µs Frequency = 30 Hz	intracranial surgery • no evidence of non-epileptic seizures • no previous left cervical vagotomy *Exclusion* Not stated		
(Chavel et al 2003) Yale University School of Medicine, New Haven, USA	Level IV Quality assessment: Good	Prospective case series	29 patients with medically refractive partial onset seizures Age range = 16-67 years Male:female = 16:13	VNS therapy plus AED therapy	*Inclusion* • older than 12 years • had medically uncontrolled partial-onset seizures with or without secondarily generalised seizures • were excluded as candidates for resective epilepsy surgery • were offered and accepted VNS treatment *Exclusion* Not stated	Effectiveness: • change in seizure frequency following VNS therapy • quality of life • number of patients with ≥50% and ≥75% reduction in seizures following VNS therapy • functionality of VNS therapy	Range = 12–24 months
(Clarke et al 1997) McMaster University Medical Centre, Ontario, Canada	Level II Quality assessment: Good	Randomised controlled trial	10 adult subjects with medically refractory complex partial epilepsy who were not suitable candidates for intracranial surgery	VNS therapy plus AED therapy Note: Two subjects received Medtronics device Model 7420	*Inclusion* • ≥6 seizures/month with no more than 14 days between seizures	*Randomised controlled trial* Effectiveness: • change in seizure frequency following VNS therapy	*Randomised controlled trial* 12 weeks

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
	Level IV Quality assessment: Good	Open label extension (case series)	Mean age = 34±8.23 years Male:female = 6:2	*High stimulation group* VNS settings: Output current = 0.25–3.5 mA Pulse width = 500 µs Frequency = 30 Hz *Low stimulation group* VNS settings: Output current = 0.5–3.0 mA Pulse width = 130 µs Frequency = 1 Hz After 12 weeks all subjects received high stimulation	• AED dosages were kept constant and maintained at therapeutic levels *Exclusion* • no evidence of other neurological disorder • pregnancy	*Case series* Effectiveness: • number of patients with ≥50% and ≥75% reduction in seizures following VNS therapy	*Case series* 50 months
(De Herdt et al 2007) Ghent University Hospital, Hôpital Universitaire Erasme Brussels, University HospitalGasthuisberg Leuven, Epilepsy Center CEPOS, Cliniques Universitaires Saint-Luc de l'Université Catholique de Louvain,	Level IV Quality assessment: Fair	Retrospective case series	138 consecutive patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 30±13 years Male:female = 67:71 Epilepsy type: Partial = 117/138 (85%) Symptomatic generalised = 21/138 (15%)	VNS therapy plus AED therapy	*Inclusion* • unsuitable candidates for resective surgery • follow-up of at least 12 months • documented seizure frequency before implantation *Exclusion* Not stated	Effectiveness: • change in seizure frequency following VNS therapy • change in AED usage	Mean = 44±27 months (range 12–120)

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
Rehabilitation and Epilepsy Center for Children and Youth Pulderbos, and Centre Hospitalier Universitaire de Liège *Possibly some overlap of patients with Boon et al (2001) and Boon et al (2002)*							
(Fai et al 2004) Chinese University of Hong Kong, Hong Kong *Include patients from study by Hsaing et al (1998)*	Level IV Quality assessment: Good	Prospective case series	13 Chinese patients with medically refractory partial-onset seizures Mean age = 25 years (range 13–40) Male:female = 6:7	VNS therapy VNS settings: Output current ≥2.5 mA On time = 30 seconds Off time = 5 minutes Pulse width = 500 ms Frequency = 30 Hz	*Inclusion* • intractable epilepsy despite adequate and appropriate treatment with at least two AEDs • age <50 years • minimum of 2 seizures per month • disconcordant or non-localising clinical, EEG and imaging data *Exclusion* • pregnancy • presence of progressive neurological disorder • systemic illness such as malignant disease	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • number of patients with ≥50% and ≥75% reduction in seizures following VNS therapy	Mean = 47±18 months

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
					• patients who were suitable candidates for intracranial surgery		
(Frost et al 2001) Children's Hospital, Boston; University of Texas Medical School, Houston; Minnesota Epilepsy Group, Minnesota; The Children's Hospital, Denver; LSU Comprehensive Epilepsy Center, Louisiana; and Children's National Medical Center, Washington DC, USA	Level IV Quality assessment: Fair	Retrospective case series	50 patients who met criteria for Lennox-Gastaut syndrome and who had been implanted with the NCP Median age = 13 years (range 5–27) <12 years: n=21 Male:female = 32:18 Ketogenic diet: n=3 Drop attacks: n=33 Previous intracranial surgery: n=6	VNS therapy plus AED therapy	*Inclusion* All patients at the study's centres who had been diagnosed with Lennox-Gastaut syndrome and implanted with the NCP system *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • quality of life • drop attacks	Range = 1–6 months
(Hallbook et al 2005b) (Hallbook et al 2005a) University Hospital, Lund Sweden	Level IV Quality assessment: Fair	Case series	15 paediatric patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates Male:female = 10:5 Median age = 11 years (range 4–17)	VNS therapy plus AED therapy VNS settings: Output current = 1–1.5 mA On time = 30 seconds Off time = 5 minutes Pulse width = 500 μs Frequency = 30 Hz	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • seizure frequency and severity following VNS therapy • quality of life • number of patients with ≥50% and ≥75% reduction in seizures following VNS therapy • drop attacks	9 months
(Holmes et al	Level IV	Prospective case	16 patients with IGE or SGE	VNS therapy plus	*Inclusion*	Safety:	Range = 12–

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
2004) University of Washington Regional Epilepsy Center, Harborview Medical Center, Seattle, USA	Quality assessment: Good	series	aged 12 years or older	AED therapy VNS settings: Output current = 1.25 mA (more if tolerated) On time = 30 seconds Off time = 5 minutes Pulse width = 500 μs Frequency = 30 Hz Magnet = 500 μs	Diagnosis of generalised epilepsy syndrome with at least 6 pharmaco-resistant seizures in the 3 months prior to enrolment. Patients were required to be on a stable regimen of at least one or more AEDs *Exclusion* Not stated	• adverse events during follow-up Effectiveness: • seizure frequency before and after VNS therapy	21 months
(Hosain et al 2000) New York Presbyterian Hospital, Cornell University, New York, USA	Level IV Quality assessment: Fair	Prospective case series	13 patients with Lennox-Gastaut syndrome All patients had severe medication resistant mixed seizures Median age = 13 years (range 4–44) Male:female = 9:4 Median AED usage = 6 (range 4–12)	VNS plus AED therapy VNS was titrated to maximum tolerable stimulation	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy	6 months
(Hsiang et al 1998) Chinese University of Hong Kong, Hong Kong	Level IV Quality assessment: Fair	Case series (unclear if retrospective or prospective)	6 Chinese patients with medically refractory partial epilepsy who were either unsuitable candidates for resective surgery or had previously failed such surgery Mean age = 22±5 years Male:female = 1:5	VNS therapy plus AED therapy VNS settings: Output current = <2 mA On time = 30 seconds Off time = 5 minutes	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy	Mean = 15±4 months (range 10–21)
(Kang et al 2006) Sang-gye Paik Hospital and	Level IV Quality assessment: Fair	Prospective case series	16 paediatric patients with medically refractory epilepsy and who were unsuitable candidates	VNS therapy plus AED therapy VNS settings:	*Inclusion* Not stated	Safety: • adverse events during follow-up	Mean = 31±21 months (range 12 months

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
Severance Hospital, Korea *Subjects also reported in You et al (2007)*			for resective surgery Mean age = 9±5 years Male:female = 8:8 Seizure type/syndrome: CPS = 3 Lennox-Gastaut syndrome = 11 severe myoclonic epilepsy in infancy = 1 Gelastic seizures originating from HH = 1	Output current = up to 3.25 mA On time = 30 seconds Off time = 5 minutes Pulse width = 500 µs Frequency = 30 Hz	*Exclusion* Not stated	Effectiveness: • change in quality of life • number of patients with ≥50% reduction in seizures following VNS therapy	– 6.6 years)
(Karceski 2001) USA	Level IV Quality assessment: Poor	Registry study	544 patients from VNS Patient Registry database who had Lennox-Gastaut syndrome and who either had no prior history of intracranial surgery or had previously had corpus callosotomy only	VNS therapy	*Inclusion* Patients with Lennox-Gastaut syndrome who had received VNS therapy *Exclusion* Not stated	Effectiveness: • number of patients with ≥50% reduction in seizures following VNS therapy	3, 6, 12 and 18 months
(Kawai et al 2002) Tokyo Metropolitan Neurological Hospital, Tokyo, Japan	Level IV Quality assessment: Fair	Prospective case series	15 patients with medically refractory partial epilepsy who had failed resective surgery or were not suitable Median age = 27 years (range 19–47)	VNS therapy plus AED therapy VNS settings: Output current = 0.25–0.75 mA On time = 30–60 seconds Off time = 5–10 minutes Pulse width = 130–1,000 µs Frequency = 20–127 Hz	*Inclusion* • medically intractable partial seizures • seizure frequency of ≥4 per month • seizure interval ≤14 days • age between 16 and 60 years *Exclusion* • previous history of vagotomy • use of an investigational AED regimen at	Safety: • adverse events during follow-up Effectiveness: • SUDEP • change in seizure frequency following VNS therapy • number of patients with ≥50% reduction in seizures following VNS therapy • change in AED usage • functionality of VNS therapy	Median = 56 months (range 48–91)

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
					time of study entry • progressive neurological diseases • unstable illness in non-neurological systems, particularly the cardiovascular and alimentary systems		
(Ko et al 1996) University of Southern California, California, USA	Level IV Quality assessment: Fair	Case series (unclear if retrospective or prospective)	3 male patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates Mean age = 41±15 years	VNS therapy plus AED therapy	*Inclusion* Not stated *Exclusion* Not stated	Effectiveness: • change in seizure frequency following VNS therapy • number of patients with ≥50% reduction in seizures following VNS therapy	Mean = 9±3 months
(Koo 2001) Children's Hospital of Pittsburgh, Pennsylvania, USA	Level IV Quality assessment: Good	Prospective case series	21 patients with medically refractory epilepsy Mean age = 14.1±7.0 years (range 4–31) Male:female = 16:5	VNS therapy plus AED therapy VNS settings: Output current = according to individual clinical needs On time = 30 seconds Off time = 5 minutes Pulse width = 500 μs Frequency = 20–30 Hz	*Inclusion* • clinically intractable epilepsy who had failed at least 3 AEDs • not candidates for intracranial surgery (with non-localising, multifocal epileptiform foci or generalised epilepsy) • opted for VNS for clinical treatment of seizures *Exclusion*	Effectiveness: • change in seizure frequency following VNS therapy	Mean = 16.8 months (range 12–23)

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
					Not stated		
(Kostov et al 2007) National Centre for Epilepsy, Oslo, Norway	Level IV Quality assessment: Fair	Prospective case series	12 patients with medically refractive idiopathic generalised epilepsy Mean age = 31±14 years (range 11–48) Male:female = 2:10	VNS therapy plus AED therapy VNS settings: Output current = 0.75–1.25 mA On time = 30 seconds Off time = 5 minutes Pulse width = 250–500 μs Frequency = 20–30 Hz	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • quality of life • number of patients with ≥50% reduction in seizures following VNS therapy • change in AED usage	Mean = 23 months (range 9–54)
(Koutroumanidis et al 2003) King's College Hospital, London, United Kingdom	Level IV Quality assessment: Fair	Case series (unclear if retrospective or prospective)	16 patients with medically refractory complex partial epilepsy who have failed previous resective surgery Mean age = 36±11.5 years (range 12–39) Male:female = 9:7	VNS therapy plus AED therapy	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy	Mean = 14±9 months (range 3–36)
(Labar et al 1998) Comprehensive Epilepsy Center, New York, USA	Level IV Quality assessment: Fair	Prospective case series	5 adult patients with medically refractive mixed symptomatic generalised epilepsy. All patients had been diagnosed with Lennox-Gastaut syndrome and one patient also had complex partial seizures. Mean age = 30±8 years Male:female = 2:3	VNS therapy plus AED therapy	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • number of patients with ≥50% or ≥75% seizure reduction	9 months
(Labar et al 1999) Cornell Medical Center, New York; Mercy Children's Hospital, MO;	Level IV Quality assessment: Good	Prospective case series	24 patients with generalised epilepsy which was medically refractory Median age = 18 years (range 4–40)	VNS therapy plus AED therapy	*Inclusion* • at least one seizure per month • age ≥3 years	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency	3 months

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
University of California, California, USA			Median AEDs = 2 (range 1–5)		• have no cardiac or progressive neurologic disease *Exclusion* Not stated	following VNS therapy • number of patients with ≥50% or ≥75% seizure reduction	
(Lundgren et al 1998a) Karolinska Hospital, Stockholm, Sweden	Level IV Quality assessment: Fair	Prospective case series	16 children with intractable epilepsy who had failed intracranial surgery or were not suitable candidates Mean age = 11 years (range 4–18) Male:female = 10:6 Previous intracranial surgery = 7 Partial epilepsy = 8 Generalised epilepsy = 8	VNS therapy plus AED therapy VNS settings: Output current = 1.5–2 mA On time = 30 seconds Off time = 3 minutes Pulse width = 500 μs Frequency = 30 Hz	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • quality of life • number of patients with ≥50% or ≥75% seizure reduction	Range = 12–24 months
(McLachlan et al 2003) University of Western Ontario, Ontario; Dalhousie University, Halifax; University of Calgary, Calgary; University of Ottawa, Ottawa; University of British Columbia, Vancouver; University of Toronto, Toronto, Canada	Level IV Quality assessment: Good	Prospective case series	27 consecutive patients with medically refractory epilepsy (localised or generalised) who had failed resective surgery or were unsuitable candidates for such surgery Mean age = 30 years (range 12–46) Male:female = 16:11	VNS therapy plus AED therapy VNS settings: Output current ≥2 mA On time = 30 seconds Off time = 3 minutes Pulse width = 500 μs Frequency = 30 Hz	*Inclusion* • seizures were uncontrolled with AEDs for 5 or more years • no progressive neurological disorder as a cause of epilepsy • resective epilepsy surgery had failed or was not an option • patients and family were motivated to try VNS therapy *Exclusion*	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • quality of life • number of patients with ≥50% seizure reduction • change in AED usage following VNS therapy	12 months

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
					Not stated		
(Majoie et al 2005) Epilepsy Centre Kempenhaeghe and University Hospital Maastricht, The Netherlands	Level IV Quality assessment: Good	Prospective case series	19 children with childhood epilepsy resembling Lennox-Gastaut syndrome Average age = 10.8 years (range 5.9–18.8) Male:female = 15:4 Confirmed Lennox-Gastaut syndrome = 13 Doose syndrome = 3 Myoclonic absence epilepsy = 1 Dravet syndrome = 2	VNS therapy plus AED therapy AED therapy: Monotherapy = 3/19 Polytherapy = 16/19 VNS device was implanted below the pectoralis major to prevent manipulation VNS settings: Output current = 1.5–2 mA On time = 30 seconds Off time = 3 minutes Pulse width = 500 µs Rapid cycling: On time = 7 seconds Off time = 18 minutes Magnets used to switch stimulation off during mealtimes in children prone to aspiration	*Inclusion* • different seizure types compatible with Lennox-Gastaut syndrome • seizures are unacceptable to patient • seizures are refractory to AEDs or side effects of effective drugs are unacceptable • patients are not eligible for resective surgery or CC • disturbed background activity and slow spike waves on EEG • moderate or mild mental handicap • age 7–18 years • written and signed informed consent of parents *Exclusion* • fast progressive neurodegenerative disease • ill health contraindicating	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • change in seizure severity • quality of life	24 months

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
					surgery • severe OPD, severe disturbances of cardiac rhythm or severe stomach disorders which contraindicate VNS		
(Marrosu et al 2003) Epilepsy Diagnostic and Treatment Centre of Cagliari, Sardinia, Italy *Overlap of patients from VNS group only in Marrosu et al (2005)*	Level III-2 Quality assessment: Fair Level IV Quality assessment: Good	Non-randomised comparative study (effectiveness) Case series (safety)	*VNS group (n=10):* Mean age = 33 years (range 23–44) Male:female = 6:4 Seizures: Complex partial *Control group – AED therapy (n=7):* Mean age = 31 years (range 21–42) Male:female = 4:3 Seizures: Not reported	*VNS group:* VNS settings: Output current = 1.75–2 mA On time = 30 seconds Off time = 5 minutes Pulse width = 500 ms Frequency = 30 Hz *Control group – AED therapy:* Continuing AED therapy. No changes to AED therapy were made in either group during this study.	*Inclusion* • relative stability of clinical features related to interictal EEG activity • refractory to classic first and second line AEDs • normal neurological and psychiatric findings • no abnormalities of cerebral structure in MRI scan *Exclusion* Not stated	Safety (case series): • adverse events during follow-up Effectiveness (non-randomised comparative study): • change in seizure frequency following VNS therapy	12 months
(Marrosu et al 2005) Epilepsy Diagnostic and Treatment Centre of Cagliari,	Level III-2 Quality assessment: Fair	Non-randomised comparative study	*VNS group (n=11):* Mean age = 34 years (range 26–44) Male:female = 6:5 Seizures: Partial	*VNS group:* VNS settings: Output current = 1.75–2 mA On time = 30 seconds	*Inclusion* • relative stability of clinical features related to interictal EEG activity • refractory to	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy	12 months

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
Sardinia, Italy *Overlap of patients from VNS group only in Marrosu et al (2003)*			*Control group – AED therapy (n=10):* Mean age = 34 years (range 23–46) Male:female = 6:4 Seizures: Partial	Off time = 5 minutes Pulse width = 500 ms Frequency = 30 Hz *Control group – AED therapy:* Continuing AED therapy	classic first and second line AEDs • normal neurological and psychiatric findings • no abnormalities of cerebral structure in MRI scan *Exclusion* Not stated		
(Morrow et al 2000) Royal Victoria Hospital, Belfast, UK	Level IV Quality assessment: Fair	Retrospective case series	10 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 32 years (range 16–54) Male:female = 9:1 Mean AEDs = 2.5 (range 1–3) Seizure type: CPS = 10 Secondary generalised = 9	VNS settings: Output current = 1–3 mA On time = 30 seconds Off time = 5 minutes Rapid cycling (offered to non-responders after 12 months) On time = 7 seconds Off time = 30 seconds	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • SUDEP • change in seizure frequency following VNS therapy • change in seizure severity following VNS therapy • quality of life • number of patients with ≥50% or ≥75% seizure reduction	Mean = 18 months (range 12–36)
(Nagarajan et al 2002) Princess Margaret Hospital, Perth, Australia	Level IV Quality assessment: Fair	Case series (unclear if retrospective or prospective)	16 children with medically refractive epilepsy who were unsuitable candidates for intracranial surgery Male:female = 9:7 Median age = 10.7 years (range 3–17) Mean AED = 2.5 Epilepsy syndrome: SGE = 7 PE = 5	VNS therapy plus AED therapy VNS settings: Output current = 1.5–2.75 mA On time = 30 seconds Off time = 3–5 minutes Pulse width = 500 µs	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • change in quality of life	Median = 25 months (range 6–47)

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
			Undetermined epilepsy = 4 Electrical SE of sleep = 1 LKS = 1	Frequency = 30 Hz Magnet used if required			
(Parker et al 1999) Guy's Hospital, London, United Kingdom	Level IV Quality assessment: Good	Prospective case series	16 consecutive children with cryptogenic epileptic encephalopathy refractory to AED therapy Mean age = 11±3 years Epilepsy syndrome: Infantile spasms developing into Lennox-Gastaut syndrome = 7 de novo Lennox-Gastaut syndrome = 3 Severe myoclonic epilepsy of infancy = 4 Myoclonic astatic epilepsy = 2	VNS therapy plus AED therapy VNS settings: Output current = 1.5–2.0 mA On time = 30 seconds Off time = 5.5 minutes Rapid cycling offered if reduction in seizure frequency was <50% at 12 months On time = 7 seconds Off time = 19 seconds	*Inclusion* All children with cryptogenic epileptic encephalopathy refractory to AED therapy implanted with VNS at Guy's Hospital 1995–96 *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • change in quality of life	6, 12 and 24 months
(Patwardhan et al 2000) Birmingham, Alabama, USA	Level IV Quality assessment: Fair	Retrospective case series	38 consecutive paediatric patients with medically refractive epilepsy Median age = 8 years (range 11 months – 17 years) Male:female = 21:17 Seizure types: Atonic = 17 GTC = 23 Absence = 17 Complex partial = 11	VNS therapy plus AED therapy	*Inclusion* • age <18 years • no anatomic or functional seizure focus amenable to resection as determined by MRI and long-term scalp or invasive intracranial EEG • seizure control refractory to multiple AEDs *Exclusion*	Safety: • adverse events during follow-up Effectiveness: • number of patients with ≥ 50% seizure reduction • quality of life	Median = 12 months (range 10–18)

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
					Not stated		
(Rizzo et al 2003) Genova, Italy	Level IV Quality assessment: Fair	Prospective case series	10 patients with refractory generalised or partial epilepsy. AED therapy remained constant throughout study. Median age = 36.5 years (range 22–43) Male:female = 7:3	VNS plus AED therapy VNS was titrated to maximum tolerable stimulation. VNS settings: Output current = 1.25–3.25 mA On time = 30–60 seconds Off time = 3–5 minutes Pulse width = 250–500 μs Frequency = 30 Hz	*Inclusion* Patients with refractory epilepsy based on clinical history and diagnostic data (EEG, CT, MRI) *Exclusion* Not stated	Effectiveness: • change in seizure frequency following VNS therapy	3 months
(Rychlicki et al 2006) G.Salesi Hospital, Ancona, Italy *Overlap of patients with Zamponi et al (2002)*	Level IV Quality assessment: Good	Prospective consecutive case series	36 children with refractory symptomatic or cryptogenic partial epilepsy Mean age = 11.5 years (range 18 months – 18 years) Male:female = 22:14 Epilepsy syndrome: PE = 27 Lennox-Gastaut syndrome = 9	VNS plus AED therapy VNS implantation: First 10 patients underwent procedure using two incisions; remaining 26 patients received only a single cervical incision	*Inclusion* • symptomatic or cryptogenic PE (with or without secondary generalisation) which is not suitable for resective surgery • absence of progressive or systemic disease • seizure frequency >10 per month and a seizure free period of <3 weeks despite AED therapy • onset of epilepsy	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy	Mean = 31 months (range 3–52)

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
					more than 3 years ago • catastrophic epilepsy in infants *Exclusion* • severe swallowing difficulties • severe mutilating behaviour • recent onset of epilepsy • progressive metabolic or degenerative disease • congenital heart defects • gastrointestinal diseases (particularly gastroesophageal reflux) • obstructive sleep apnoeas • poor parental compliance		
(Saneto et al 2006) Children's Hospital and Regional Medical Center, Washington, USA *Some subjects are also included in study by Arthur et*	Level IV Quality assessment: Fair	Retrospective case series	63 children aged less than 12 years, implanted with VNS. 43 subjects provided data relating to effectiveness outcomes. Mean age = 8 years (range 2.6–11.9) Male:female = 24:19	VNS plus AED therapy VNS settings: Median output current = 1.75 mA On time = 30 seconds Off time = 3 minutes	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy (43 subjects provided data relating to effectiveness outcomes)	Range = 6–18 months

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
al (2007)			14 patients had been on the ketogenic diet previously and 4 patients were on the diet at implantation. Mean AEDs = 2.6±1.0 (range 1–5) Seizure types: Generalised = 20 Partial = 8 Mixed = 15				
(Smyth et al 2003)	Level IV Quality assessment: Good	Retrospective case series	74 consecutive paediatric patients with medically refractory multifocal or generalised epilepsy Mean age = 8.8 years (range 11 months – 18 years) Male:female = 41:33	VNS plus AED therapy	*Inclusion* • ≤18 years of age at time of implantation • minimum follow-up of 12 months • medically refractory, multifocal or generalised epilepsy *Exclusion* Not stated	Safety: • adverse events during follow-up	Minimum = 12 months Mean = 2.2 years
(Tanganelli et al 2002) Genoa, Italy	Level IV Quality assessment: Fair	Prospective case series	47 patients with medically refractory epilepsy without indication for resective surgery Mean age = 29 years (range 7–49) Male:female = 28:19 Epilepsy type/syndrome: Partial epilepsy with SGS = 22 Partial epilepsy without SGS = 13 Lennox-Gastaut syndrome = 12	VNS therapy: Output current = 0.5–3.5 mA On time = 30 seconds Off time = 5 minutes If no response in after 3 months then rapid cycling: On time = 7 seconds Off time =	*Inclusion* • epileptic seizures refractory to both old and new AEDs • without indication for resective surgery *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • number of patients with ≥50% and ≥75% reduction in seizures following VNS therapy	Mean = 26 months (range 6–50)

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
				21 seconds Or On time = 1 minute Off time = 5 minutes Or On time = 1 minute Off time = 3 minutes			
(Uthman et al 1993) **(Penry & Dean 1990)** **(Uthman et al 1990)** Department of Veterans Affairs Medical Center, Florida, USA	Level IV Quality assessment: Good	Prospective case series	15 patients with medically refractory partial seizures Age range = 18–58 years Male:female = 9:6 EO1 study (n=11) EO2 study (n=4)	VNS plus AED therapy	*Inclusion* • at least a 1-year documented seizure history • >18 years of age *Exclusion* • status epilepticus in previous 2 years • progressive neurologic or systemic disorders • treatable underlying aetiology • mental retardation • drug abuse, asthma, gastritis, gastric or duodenal ulcers, insulin-dependent diabetes • prior vagotomy procedure	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • number of patients with ≥50% and ≥75% reduction in seizures following VNS therapy	Mean = 25 months (range 14–36)
(Vonck et al 2004) Ghent University Hospital, Belgium;	Level IV Quality assessment: Fair	Retrospective case series	118 patients with medically refractory epilepsy who were not suitable candidates for resective surgery	VNS therapy plus AED therapy *Ghent University*	*Inclusion* Not stated *Exclusion*	Safety: • adverse events during follow-up Effectiveness:	Mean = 33 months (range 6–94)

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
Dartmouth-Hitchcock Medical Center, New Hampshire, USA *Possible overlap with Boon et al (2001) and Boon et al (2002)*			Mean age = 32 years (range 4–59) Ghent University Hospital: n=61 Male:female = 32:29 Dartmouth-Hitchcock Medical Center: n=57 Male:female = 33:24 Prominent seizure type: CPS±SGS = 95 GE = 18 SPS = 5	*Hospital:* Output current = 1.8 mA (range 0.5–2.75) On time = 30 seconds Off time = 1 minute Pulse width = 500 µs Frequency = 30 Hz Dartmouth-Hitchcock Medical Center: Output current = 1.0 mA (range 0.5–2.0) On time = 30 seconds Off time = 5 minutes Pulse width = 250 µs Frequency = 30 Hz	Not stated	• change in seizure frequency following VNS therapy • number of patients with ≥50% reduction in seizures following VNS therapy	
(You et al 2007) Epilepsy Centers of Sanggye Paik Hospital, Asan Medical Center and Severance Hospital, Korea *Subjects also reported in Kang et al (2006)*	Level IV Quality assessment: Fair	Retrospective case series	28 paediatric patients with medically refractory epilepsy. All patients had either multifocal or generalised epilepsy and were therefore unsuitable candidates for resective surgery. Mean age = 9.3±3.9 years Male:female = 16:12 Epilepsy syndrome/type: Lennox-Gastaut syndrome = 14 Unclassified generalised seizures = 2 Severe myoclonic epilepsy in	VNS plus AED therapy	*Inclusion* Not stated *Exclusion* Not stated	Safety: • adverse events during follow-up Effectiveness: • quality of life • number of patients with ≥50% reduction in seizures following VNS therapy	Mean = 31±19 months (range 12 months – 7.7 years)

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
			infancy = 1 Secondary generalised tonic-clonic seizures = 10 Gelastic seizures with hypothalamic hamartoma = 1				
(Zamponi et al 2002) G.Salesi Hospital, Ancona, Italy *Overlap of patients with Rychlicki et al (2006)*	Level IV Quality assessment: Good	Prospective case series	13 children with refractory symptomatic or cryptogenic partial epilepsy Mean age = 10.5 years (range 1.4–17) Male:female = 7:6 Symptomatic PE = 10 Cryptogenic PE = 3	VNS plus AED therapy VNS settings: Output current = 2 mA On time = 30 seconds Off time = 5 minutes Frequency = 30 Hz Rapid cycling (3 patients) On time = 7 seconds Off time = 20 seconds	*Inclusion* • symptomatic or cryptogenic PE (with or without secondary generalisation) which is not suitable for resective surgery • absence of progressive or systemic disease • seizure frequency >10 per month and a seizure free period of <3 weeks despite AED therapy • onset of epilepsy more than 3 years ago • catastrophic epilepsy in infants *Exclusion* • severe swallowing difficulties • severe mutilating behaviour • recent onset of epilepsy	Safety: • adverse events during follow-up Effectiveness: • change in seizure frequency following VNS therapy • quality of life • number of patients with ≥50% reduction in seizures following VNS therapy	Mean = 13.6 months (range 6–22) 8 patients had a follow-up period of more than 12 months

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
					• progressive metabolic or degenerative disease • congenital heart defects • gastrointestinal diseases (particularly gastro-oesophageal reflux) • obstructive sleep apnoeas • poor parental compliance		

AED = anti-epileptic drug; CC = corpus callosotomy; CPS = complex partial seizures; CT = computed tomography; EEG = electroencephalogram; EOES = end of effective stimulation; EOBL = end of effective battery life; GTC = generalised tonic-clonic; HH = hypothalamic hamartoma; Hz = hertz; IGE = idiopathic generalised epilepsy; LKS = Landau-Kleffner syndrome; PE = partial epilepsy; mA = milliamperes; MRI = magnetic resonance imaging; MST = multiple subpial transaction; NCP = NeuroCybernetic Prosthesis; OPD = obstructive pulmonary disease; SD = standard deviation; SE = status epilepticus; SGE = symptomatic generalised epilepsy; SGS = secondarily generalised seizures; SPS = simple partial seizures; VNS = vagus nerve stimulation

Study profiles of included case reports

Study	Level of evidence	Location	Study design	Study participants	Intervention	Outcomes assessed	Duration of follow-up
(Akman et al 2003)	N/A	Children's Hospital of New York, New York, USA	Case report	21-year-old male with seizures of a bilateral temporal onset. Seizures were refractory to AED therapy.	VNS therapy plus AED therapy VNS settings: Output current = 0.5–2.0 mA On time = 30 seconds Off time = 5 minutes	Safety: • adverse events during follow-up	2 years
(Ali et al 2004)	N/A	Medical College of Ohio, Ohio, USA	Case studies	Patient 1: 53-year-old male with refractory generalised seizures Patient 2: 40-year-old male with refractory mixed seizures *Note: Third patient reported, but did not meet inclusion criteria for this review*	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	Not reported
(Amark et al 2007)	N/A	Karolinska Hospital, Stockholm, Sweden	Case report	17-year-old male with complex partial seizures with and without secondary generalisation. After presurgical evaluation, patient was considered suitable for VNS therapy.	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	2 years 4 months
(Ardesch et al 2007a)	N/A	Medisch Spectrum Twente, Enschede, The Netherlands	Case studies	Patient 1: 32-year-old female with medically refractory complex partial seizures. MRI did not show structural lesions. Patient 2: 52-year-old male with medically refractory partial seizures. No abnormalities found on MRI. No cardiac history was reported. Patient 3: 59-year-old female with tonic-clonic seizures. MRI showed bilateral temporal sclerosis. Patient had no cardiac history.	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	Patient 1: 6 years Patient 2: 6 years Patient 3: 3 years

(Bernards 2004)	N/A	University of Washington, Washington, USA	Case report	54-year-old female with idiopathic complex partial seizures	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	2 years
(Boon et al 2001a)	N/A	Ghent University Hospital, Belgium	Case studies	Patient 1: 36-year-old female with complex partial seizures with occasional secondary generalisation. Patient was considered unsuitable for resective surgery. Patient 2: 35-year-old female with complex partial seizures with occasional secondary generalisation. Patient was considered unsuitable for resective surgery. *Note: Third patient reported, but no safety data was reported*	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	Patient 1: Not reported Patient 2: 5 years
(Buoni et al 2004b)	N/A	University of Siena, Italy	Case report	22-year-old male with Lennox-Gastaut syndrome	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	3 years
(Carius & Schulze-Bonhage 2005)	N/A	University Hospital of Freiburg, Germany	Case studies	Patient 1: 43-year-old female with cryptogenic partial epilepsy who was not a suitable candidate for resective surgery Patient 2: 51-year-old female with symptomatic partial epilepsy who was not a suitable candidate for resective surgery Patient 3: 48-year-old male with multifocal symptomatic epilepsy	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	Patient 1: 1 year Patient 2: 3 months Patient 3: 11 months
(Duhaime et al 2000)	N/A	Children's Hospital of Philadelphia, Pennsylvania, USA	Case report	16-year-old female with medically refractory simple and complex partial seizures Previous history of generalised tonic-clonic seizures Previous multiple subpial resection had left patient seizure free for 2 weeks, after which	VNS therapy plus AED therapy VNS settings: Output current = 1.5 mA On time = 30 seconds Off time = 5 minutes	Safety: • adverse events during follow-up	10 months

				habitual seizures returned.	Pulse width = 500 µs Frequency = 30 Hz		
(Gatzonis et al 2000)	N/A	Eginition Hospital, Athens, Greece	Case report	35-year-old male with refractory left frontotemporal epileptic seizures. High resolution MRI was normal.	VNS therapy plus AED therapy VNS settings: Output current = 1.5 mA On time = 30 seconds Off time = 5 minutes Pulse width = 500 µs Frequency = 30 Hz	Safety: • adverse events during follow-up	4 months
(Holmes et al 2003)	N/A	University of Washington School of Medicine, Washington, USA	Case report	21-year-old female with medically refractory primary generalised epilepsy	VNS therapy plus AED therapy VNS settings: Output current = 3.25 mA On time = 300 seconds Off time = 30 seconds Pulse width = 500 µs Frequency = 30 Hz	Safety: • adverse events during follow-up	Not reported
(Iriarte et al 2001)	N/A	University of Navarra, Pamplona, Spain	Case report	20-year-old male with tuberous sclerosis. Seizures included various complex partial and secondarily generalised tonic-clonic seizures and were unsuitable for resective surgery.	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	8 weeks
(Kalkanis et al 2002)	N/A	Southern Illinois University School of Medicine, Illinois, USA	Case report	25-year-old male with refractory tonic-clonic seizures of multifocal origin *Note: Second patient reported, but did not meet inclusion criteria for this review*	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	Several months
(Labar & Ponticello 2003)	N/A	New York Presbyterian-Weill Cornell Medical Center, New York, USA	Case report	22-year-old male with medication resistant mixed seizures. Previous history of corpus callosotomy	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	6 years
(Leijten & Van Rijen 1998)	N/A	University Hospital, Utrecht, The Netherlands	Case report	42-year-old male with medically refractory epilepsy of multilobar, left-sided onset. Patient was considered unsuitable for intracranial	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	Not reported

				surgery.			
(McGregor et al 2005)	N/A	Texas Comprehensive Epilepsy Program, Texas, USA	Case studies	Patient 1: Male child with symptomatic mixed generalised seizures Patient 2: Male child with generalised tonic-clonic, complex partial and atonic seizures Patient 3: Male child with intractable symptomatic mixed seizure disorder secondary to congenital brain malformation	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	Patient 1: 3.4 years Patient 2: 4.5 years Patient 3: 12 months
(Ortler et al 2001)	N/A	Innsbruck, Austria	Case report	35-year-old male with complex partial seizures with secondary generalisation. Patient was not considered to be a suitable candidate for resective surgery.	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	1 year
(Papacostas et al 2007)	N/A	Cyprus Institute of Neurology & Genetics, Nicosia, Cyprus	Case report	19-year-old female with complex partial seizures. Seizures were refractory to AED therapy and not suitable for resective surgery.	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	2 years
(Patel & Edwards 2004)	N/A	Baylor College of Medicine, Texas, USA	Case report	6-year-old male with cryptogenic epilepsy	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	5 months
(Rauchenzauner et al 2007)	N/A	Medical University Innsbruck, Austria	Case report	4-year-old with medically refractory idiopathic generalised epilepsy	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	1 year
(Sanossian & Haut 2002)	N/A	Montefiore Medical Center, New York, USA	Case report	35-year-old male with complex partial seizures refractory to AED therapy. Patient was an unsuitable candidate for resective surgery.	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	≥ 1 month
(Tatum Iv et al 1999)	N/A	University of South Florida, Florida, USA	Case studies	Patient 1: 38-year-old female with multifocal complex partial epilepsy Patient 2:	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	Patient 1: Not reported Patient 2: Not reported

				57-year-old male with medically refractory partial epilepsy who was unsuitable for resective surgery Patient 3: 38-year-old male with multifocal partial epilepsy Patient 4: 42-year-old male medically refractory partial epilepsy who was unsuitable for resective surgery			Patient 3: Not reported Patient 4: 9 months
(Vassilyadi & Strawsburg 2003)	N/A	Children's Hospital Medical Center, Ohio, USA	Case report	3-year-old male with mixed seizures	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	6 months
(Zalvan et al 2003)	N/A	Beth Israel Medical Center, New York, USA	Case report	Patient 1: 19-year-old male with partial complex seizures. MRI was normal, EEG indicated a non-specific bifrontal focus and SPECT was equivocal. Patient 2: 28-year-old male with medically refractory complex partial seizures suggestive of nocturnal frontal lobe epilepsy (non-lateralisable) Patient 3: 2-year-old female with mental retardation and cerebral palsy. EEG demonstrated bilateral discharges, MRI was normal. Seizures were refractory to AED therapy. Patient 4: 10-year-old female with Lennox-Gastaut syndrome refractory to AED therapy. History of cerebral palsy and spastic quadriplegia	VNS therapy plus AED therapy	Safety: • adverse events during follow-up	Patient 1: 1 year Patient 2: ≥3 months Patient 3: 1 month Patient 4: 7 months
(Zumsteg et al 2000)	N/A	University Hospital Zurich, Switzerland	Case report	Patient 1: 28-year-old male with simple and complex partial seizures of unknown origin Patient 2: 34-year-old female with medically refractory mesiobasal limbic epilepsy with bilateral	VNS therapy plus AED therapy Patient 1 - VNS settings: Output current = 1.0 mA On time = 60 seconds	Safety: • adverse events during follow-up	Patient 1: 17 weeks Patient 2: 19 weeks Patient 3: 12 weeks

				onset. Patient 3: 26-year-old patient with complex partial seizures. Previous history of amygdalohippocampectomy for a palliative indication.	Off time = 5 minutes Pulse width = 500 µs Frequency = 30 Hz Patient 2 – VNS settings: Output current ≥2 mA Patient 3 – VNS settings: Output current = 0.75 mA		

AED = anti-epileptic drug; EEG = electroencephalogram; MRI = magnetic resonance imaging; SPECT = single photon emission computed tomography; VNS = vagus nerve stimulation

Appendix E Safety results from included case reports

Table 55 Adverse events in both adults and children reported in case reports

Study	Study design	Study participants	Adverse events
Partial epilepsies			
(Akman et al 2003)	Case report	21-year-old male with seizures of a bilateral temporal onset.	Tightness in throat, stomach and upper chest during stimulation
(Amark et al 2007)	Case report	17-year-old male with complex partial seizures with and without secondary generalisation	Regular episodes of bradycardia and asystole presenting as drop attacks. Drop attacks ceased immediately following cessation of stimulation. VNS generator was explanted, in which no abnormalities were found.
(Bernards 2004)	Case report	54-year-old female with idiopathic complex partial seizures	Patient was undergoing reduction and internal fixation of an isolated trimalleolar ankle fracture. Patient had VNS implanted 2 years previously. Following insertion of laryngeal mask airway, inspiratory stridor and sternal retractions were noted. Positive pressure was applied, which reduced symptoms markedly. Apparent partial obstruction spontaneously resolved after 1 minute. Partial obstruction and stridor occurred 5 minutes later, with this patterning continuing over 40 minutes. Review of records showed that pattern of stimulation matched that of intermittent partial obstruction.
(Boon et al 2001a)	Case studies	Patient 1: 36-year-old female with complex partial seizures with occasional secondary generalisation Patient 2: 35-year-old female with complex partial seizures with occasional secondary generalisation	Patient 1: Mild and intermittent hoarseness during ramp-up period Patient 2: Hoarseness during stimulation
(Buoni et al 2004b)	Case report	22-year-old male with Lennox-Gastaut syndrome	Anorexia and headache upon increasing output current to 0.75 mA
(Carius & Schulze-Bonhage 2005)	Case studies	Patient 1: 43-year-old female with cryptogenic partial epilepsy Patient 2: 51-year-old female with symptomatic partial epilepsy Patient 3: 48-year-old male with multifocal symptomatic epilepsy	Patient 1: Intense pain shooting into left lower jaw during stimulation. Between stimulation periods, patient experienced decreased sensation in lower left jaw and slight pain in left ear. Patient 2: Toothache in left lower jaw and occipital headaches during stimulation. Patient also reported sore throat on left side. Patient 3: Slight pulling pain in left lower jaw during stimulation
(Gatzonis et al 2000)	Case report	35-year-old male with refractory left frontotemporal epileptic seizures	After 2 months of VNS therapy, family noted change in behaviour. Psychiatric evaluation noted schizophrenia-like symptoms.

Study	Study design	Study participants	Adverse events
(Iriarte et al 2001)	Case report	20-year-old male with tuberous sclerosis. Seizures included various complex partial and secondarily generalised tonic-clonic seizures.	Episodic cervical pain on left side with change in posture, flexion and mild rotation of the head to the right. Patient also experienced coughing and voice alteration.
(Kalkanis et al 2002)	Case report	25-year-old male with refractory tonic-clonic seizures of multifocal origin	No surgical complications. Sudden and persistent hoarseness reported 6 weeks after implantation. Caregivers reported the patient had 'flipped the device under his skin'. X-ray indicated a twisted stimulator lead requiring replacement. Hoarseness improved only following thyroplasty.
(Leijten & Van Rijen 1998)	Case report	42-year-old male with medically refractory epilepsy of multilobar, left-sided onset	Hoarseness and tingling in throat during stimulation. As current increased to 2.0 mA, patient reported tightness in chest and dyspnoea during stimulation when lying supine and head turned to left. X-ray confirmed tonic contraction of hemidiaphragm.
(Ortler et al 2001)	Case report	35-year-old male with complex partial seizures with secondary generalisation	Cervical wound infection 5 weeks post-implantation during which perioperative antibiotics were not applied. Wound revision was required 2 months later.
(Papacostas et al 2007)	Case report	19-year-old female with complex partial seizures	Coughing upon initial activation. At 2 years follow-up caregiver reported episodes of breathlessness during sleep. Polysomnography indicated centrally induced sleep apnoeas. Clinical apnoea decreased upon reduction of stimulation parameters.
(Patel & Edwards 2004)	Case report	6-year-old male with cryptogenic epilepsy	Patient presented with infection 2 weeks after implantation. Infection was found to be due to MSSA. IV antibiotics were followed by home therapy. One week later patient presented with surgical wound dehiscence. Stimulator was explanted, cleaned and replaced. MSSA was subsequently cultured from wound site. Before completion of antibiotic therapy, inflammation developed around implantation site. Generator was explanted and culture of pocket site grew MSSA. Subsequent inflammation of pocket site following IV therapy prompted removal of leads.
(Sanossian & Haut 2002)	Case report	35-year-old male with complex partial seizures refractory to AED therapy	3 weeks post-implantation patient reported severe diarrhoea with exacerbation of pre-existing haemorrhoids. Persistent diarrhoea resulted in anaemia. Full gastrointestinal evaluation was significant only for haemorrhoids. Termination of stimulation resulted in resolution of diarrhoeal symptoms.
(Tatum Iv et al 1999)	Case studies	Patient 1: 38-year-old female with multifocal complex partial epilepsy Patient 2: 57-year-old male with medically refractory partial epilepsy who was unsuitable for resective surgery Patient 3: 38-year-old male with multifocal partial epilepsy	Patient 1: Repeated intraoperative testing produced ventricular asystole. Implantation of VNS device was aborted. Patient 2: Repeated intraoperative testing produced bradycardia followed by ventricular asystole on a third test. Implantation of VNS device was aborted. Patient 3: Initial intraoperative testing produced bradycardia to asystole for 10 seconds. Alternative VNS generator testing produced no abnormalities. Rechallenge with first generator

Study	Study design	Study participants	Adverse events
		Patient 4: 42-year-old male with medically refractory partial epilepsy who was unsuitable for resective surgery	produced atrioventricular block. Implantation was aborted. Patient 4: Initial intraoperative testing produced cardiac asystole for 45 seconds. Further testing with increasing current resulted in no heart rate change. Implantation proceeded without further consequence.
(Zumsteg et al 2000)	Case studies	Patient 1: 28-year-old male with simple and complex partial seizures of unknown origin Patient 2: 34-year-old female with medically refractory mesiobasal limbic epilepsy with bilateral onset Patient 3: 26-year-old patient with complex partial seizures. Previous history of amygdalohippocampectomy for a palliative indication	Patient 1: Mild and well-tolerated hoarseness and cough at 1 month. At day 118, patient experienced acute and severe dyspnoea and nausea during stimulation due to left vocal cord adduction. Patient 2: Intermittent, mild voice alteration and discomfort in neck during stimulation resulting from left vocal cord adduction. Patient 3: After 2 months of VNS therapy, patient reported intermittent mild voice alteration and shortness of breath upon exertion.
Generalised epilepsies			
(Holmes et al 2003)	Case report	21-year-old female with medically refractory primary generalised epilepsy	Excessive drowsiness and unintentionally falling asleep at inopportune times. Frequent breathing pauses during sleep were witnessed by family. Pauses lasted up to 30 seconds and occurred 4–6 times per half hour.
(Rauchenzauner et al 2007)	Case report	4-year-old with medically refractory idiopathic generalised epilepsy	No adverse events
Partial and generalised epilepsies			
(Ali et al 2004)	Case studies	Patient 1: 53-year-old male with refractory generalised seizures Patient 2: 40-year-old male with refractory mixed seizures	Patient 1: Complete heart block with ventricular asystole during intraoperative testing. Repeated testing had same result. VNS device was removed with no sequelae. Patient 2: Ventricular asystole during intraoperative testing. VNS device was removed with no sequelae.
(Ardesch et al 2007a)		Patient 1: 32-year-old female with medically refractory complex partial seizures Patient 2: 52-year-old male with medically refractory partial seizures Patient 3: 59-year-old female with tonic-clonic seizures	Patient 1: Bradycardia during repeated intraoperative testing. Implantation proceeded and patient reported hoarseness, coughing and paraesthesia during stimulation. Patient 2: Repeated intraoperative testing resulted in bradycardia. Implantation proceeded and subsequent 24-hour ECG noted first degree AV block during night-time period with sinus bradycardia within normal variation. Voice alterations were reported post-operatively and examination showed left vocal cord paralysis. During generator replacement due to battery depletion, no adverse events occurred subsequent to intraoperative testing. Patient 3:

Study	Study design	Study participants	Adverse events
			Repeated intraoperative testing resulted in bradycardia. No changes in cardiac rhythm were detected following initiation of VNS therapy.
(Duhaime et al 2000)	Case report	16-year-old female with medically refractory simple and complex partial seizures	Voice alteration during stimulation. At 8 weeks, spontaneous onset of severe, lancinating pain in left tonsil. Pain intensified by swallowing. Symptoms continued only during stimulation. Stimulation was terminated, followed by reduction in stimulation intensity.
(Labar & Ponticello 2003)	Case report	22-year-old male with medication-resistant mixed seizures. Previous history of corpus callosotomy	Infection following VNS generator replacement (due to end of battery life), requiring removal of device
(McGregor et al 2005)	Case studies	Patient 1: Male child with symptomatic mixed generalised seizures Patient 2: Male child with generalised tonic-clonic, complex partial and atonic seizures Patient 3: Male child with intractable symptomatic mixed seizure disorder secondary to congenital brain malformation	Patient 1: Implantation and subsequent removal of VNS device 3 times due to infection and skin breakdown Patient 2: Fractured lead wire requiring replacement. Infection followed as did removal of the VNS device. Subsequent implantation of VNS occurred on right side. Patient experienced exercise-induced reactive airway disease not responsive to anti-cholinergic agent. Stimulation was terminated and left sided VNS re-implanted and therapy initiated. Patient 3: Removal of VNS device due to post-operative infection. Another VNS device was implanted and again required removal due to infection. Right-sided VNS was implanted. Caregiver reported transient voice alteration and wheezing.
(Vassilyadi & Strawsburg 2003)	Case report	3-year-old male with mixed seizures	Infection 2 weeks post-implantation requiring IV antibiotics. VNS leads began to extrude from incision site. Removal of VNS device and leads was performed. 10 days later, caregivers noticed voice alteration and coughing and gagging during meals. Chest X-ray identified left vocal cord paralysis.
(Zalvan et al 2003)	Case studies	Patient 1: 19-year-old male with partial complex seizures Patient 2: 28-year-old male with medically refractory complex partial seizures suggestive of nocturnal frontal lobe epilepsy (non-lateralisable) Patient 3: 2-year-old female with mental retardation and cerebral palsy Patient 4: 10-year-old female with Lennox-Gastaut syndrome refractory to AED therapy	Patient 1: Patient noted hoarseness, breathiness and ineffective cough after implantation. Left vocal cord paresis was demonstrated 2 weeks later with some pooling of secretions in left pyriform sinus. Patient also reported increased frequency of hiccoughs, intermittent dysphagia associated with mild aspiration during stimulation. Sensation of jaw being pulled downward on left side during stimulation was also reported. Patient 2: Voice alteration immediately following implantation. Dyspnoea upon exertion was reported 5 days after implantation (before activation of stimulator) due to left vocal cord paresis. Patient 3: Inspiratory stridor and coughing associated

Study	Study design	Study participants	Adverse events
			with drinking, as well as intermittent episodes of grunting and feeding difficulty. Examination demonstrated immobile left vocal fold. Patient 4: Aphonia for 2 months following implantation. Caregiver noted difficulty in handling secretions, particularly at night, resulting in coughing and gagging. Examination noted immobile left vocal cord.

VNS = vagus nerve stimulation; AED = anti-epileptic drug; IV = intravenous; MSSA = methicillin-sensitive *Staphylococcus aureus*

Appendix F Effectiveness results

Table 56 Change in seizure frequency following VNS therapy in adults

Study	Study design and quality appraisal	Population	Follow-up period	Absolute seizure frequency (seizures per month) Mean±SD		
				Baseline	**Follow-up**	**Mean percentage change[a]**
Partial epilepsies						
(Clarke et al 1997)	Level II (randomised controlled trial) and Level IV (case series) Quality assessment: Level II: Good Level IV: Good	10 adult subjects with medically refractory complex partial epilepsy who were not suitable candidates for intracranial surgery	Randomised controlled trial = 12 weeks Case series = 50 months	*High stimulation:* Not reported *Low stimulation:* Not reported	*High stimulation:* Not reported *Low stimulation:* Not reported	*Randomised controlled trial:* *High stimulation:* 50%[d] *Low stimulation:* 8%[d] *Case series:* 55±39%
(Boon et al 2002) *Overlap of patients with Boon et al (2001)*	Level III-2 non-randomised comparative study Quality assessment: Fair	84 consecutive patients with partial epilepsy. Patients underwent pre-surgical evaluation and were assigned to appropriate treatment group by multidisciplinary team *VNS group:* (n=25) *Comparator:* AED therapy (n=25) Mean age = 32 years (range 5–71)	Mean = 26 months (range 12–57)	*VNS* 28±50 *AED therapy* 12±11	*VNS* 9±13 *AED therapy* 9±11	*VNS* 70±26%[g] (p<0.05)[b] *AED therapy* 22±48%[g] (NS)[b]
(Marrosu et al 2005)	Level III-2 non-randomised, comparative study Quality assessment: Fair	21 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery *VNS group:* (n=11) *Comparator:* AED therapy (n=10)	12 months	*VNS* 151±46 *AED therapy* 13±5	*VNS* 97±65 *AED therapy* 3±2	*VNS* 39±29%[g d] *AED therapy* 76±1%[g d]
(Marrosu et al 2003)	Level III-2 non-randomised,	17 patients with medically refractory	12 months	*VNS* 39±10	*VNS* 25±19	*VNS* 41±36%[d]

Study	Study design and quality appraisal	Population	Follow-up period	Absolute seizure frequency (seizures per month) Mean±SD		
				Baseline	**Follow-up**	**Mean percentage change[a]**
	comparative study Quality assessment: Fair	epilepsy who were unsuitable candidates for resective surgery *VNS group:* n=10 *Comparator:* AED therapy (n=7)		*AED therapy* 38±10	*AED therapy* 36±14	*AED therapy* 6±15%[d]
(Alsaadi et al 2001)	Level IV case series Quality assessment: Good	10 adult patients with bilateral independent temporal lobe epilepsy. Patients were medically refractory and had failed intracranial surgery or were not considered suitable candidates	12 months	Not reported	Not reported	51±25%
(Chavel et al 2003)	Level IV case series Quality assessment: Good	29 patients with medically refractive partial onset seizures	12–24 months	30.1±35.2	12 months (n=25): 14±18.9 24 months (n=23): 16.3±27.5	12 months (n=25): 53% p<0.05 24 months (n=23): 46% p<0.05
(Fai et al 2004)	Level IV case series Quality assessment: Good	13 Chinese patients with medically refractory partial-onset seizures Mean age = 25 years (range 13–40)	Mean = 47±18 months	26	6 months: 18 12 months: 13 18 months: 15	6 months: 33±37%[g] 12 months: 47±34%[g] 18 months: 35±33%[g]
(Uthman et al 1993) (Penry & Dean 1990) (Uthman et al 1990)	Level IV case series Quality assessment: Good	15 patients with medically refractory partial seizures EO1 study (n=11) EO2 study (n=4)	Mean = 25 months (range 14–36)	64±182	Not reported	47%
(Ardesch et al 2007b)	Level IV case series Quality assessment: Fair	19 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Up to 6 years	28±35	Not reported	1 year: 14% (n=19) 2 year: 25%[f] (n=19) 3 year: 29%[f] (n=16) 4 year: 29%[f] (n=15)

Study	Study design and quality appraisal	Population	Follow-up period	Absolute seizure frequency (seizures per month) Mean±SD		
				Baseline	Follow-up	Mean percentage change[a]
						5 year: 43%[f] (n=9) 6 year: 50%[f] (n=7)
(Kawai et al 2002)	Level IV case series Quality assessment: Fair	15 patients with medically refractory partial epilepsy who had failed resective surgery or were not suitable candidates	Median = 56 months (range 48–91)	58±65	Not reported	1 year (n=13): 28±42% 2 year (n=13): 47±52% 3 year (n=13): 54±54% 4 year (n=13): 63±37% 5 year (n=6): 78±18% 6 year (n=5): 65±28% 7 year (n=2): 55±21%
(Ko et al 1996)	Level IV case series Quality assessment: Fair	3 male patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	Mean±SD = 9±3 months	104±161	38±43	9±54%[g] Median = (–10%) (range (–33)–70)
(Koutroumanidis et al 2003)	Level IV case series Quality assessment: Fair	16 patients with medically refractory complex partial epilepsy who have failed previous resective surgery Mean age ± SD = 36 ±11.5 years (range 12–39)	Mean±SD = 14±9 months (range 3–36)	37±56	28±34	–9±105%[g] Median = 0% (range (–391)–83)
(Morrow et al 2000)	Level IV case series Quality assessment: Fair	10 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 32 years (range 16–54)	Mean = 18 months (range 12–36)	15 (range 5–52)	Not reported	Approximately 30%
(Brazdil et al 2001)	Level IV case series Quality assessment: Poor	12 adult patients with medically refractory focal or multifocal epilepsy. Patients had	6 months	Not reported	Not reported	31±26%[g] (range 0–75)

Study	Study design and quality appraisal	Population	Follow-up period	Absolute seizure frequency (seizures per month) Mean±SD		
				Baseline	Follow-up	Mean percentage change[a]
		been assessed and found to be unsuitable candidates for resective surgery.				
Generalised epilepsies						
(Holmes et al 2004)	Level IV case series Quality assessment: Good	16 patients with IGE or SGE aged 12 years or older	12–21 months	198±226	107±161	43±42%[g], p=0.002[b]
(Labar et al 1999)	Level IV case series Quality assessment: Good	24 patients with generalised epilepsy which was medically refractory	3 months	Median = 48 (range 2–1,650)	Not reported	Median = 46% (range 85 – (–30), p<0.05
(Kostov et al 2007)	Level IV case series Quality assessment: Fair	12 patients with medically refractory idiopathic generalised epilepsy Mean age±SD = 31±14 years (range 11–48)	Mean = 23 months (range 9–54)	Not reported	Not reported	61%, p<0.05[b]
(Labar et al 1998)	Level IV case series Quality assessment: Fair	5 adults with medically refractory mixed symptomatic generalised epilepsy. All patients had been diagnosed with Lennox-Gastaut syndrome and one patient also had complex partial seizures.	9 months	74±35	28±21	59±25%[g], p<0.05[c]
Partial and generalised epilepsies						
(McLachlan et al 2003)	Level IV case series Quality assessment: Good	27 consecutive patients with medically refractory epilepsy (localised or generalised) who had failed resective surgery or were unsuitable candidates for such surgery Mean age =	12 months	Not reported	Not reported	29%

Study	Study design and quality appraisal	Population	Follow-up period	Absolute seizure frequency (seizures per month) Mean±SD		
				Baseline	Follow-up	Mean percentage change[a]
		30 years (range 12–46)				
(Amar et al 2004)	Level IV case series Quality assessment: Fair	921 patients from the VNS patient registry who had been implanted with the VNS device Median age = 28 years (range 1–66)	Up to 24 months	Not reported	Not reported	6 months: 43% 12 months: 46% 18 months: 52% 24 months: 51%
(Boon et al 2001b) *Overlap of patients with Boon et al (2002)*	Level IV case series Quality assessment: Fair	35 patients with partial seizures or Lennox-Gastaut syndrome who were refractory to AEDs and were unsuitable candidates for resective surgery	Mean±SD = 35 months (range 9–73)	32±49	11±15	57±30%[g], p<0.005[b]
(Chayasirisobhon et al 2003)	Level IV case series Quality assessment: Fair	34 patients with medically refractory epilepsy who were unsuitable for resective surgery Mean age = 27.6 years (range 5–70)	6 months	136±298	33±43	55±35%[g]
(De Herdt et al 2007) *Possibly some overlap of patients with Boon et al (2001) and Boon et al (2002)*	Level IV case series Quality assessment: Fair	138 consecutive patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 30±13 years (range 4–59)	Mean = 44±27 months (range 12–120)	Overall: 41±61 Children vs adults: 71 v 36 PE v SGE: 33 v 85	Overall: 7±25 Children vs adults: 30 v 14 PE v SGE: 14 v 29	Overall: 51% p<0.001[b] Children vs adults: 41% v 53% PE v SGE: 50% v 56%
(Rizzo et al 2003)	Level IV case series Quality assessment: Fair	10 patients with refractory generalised or partial epilepsy Median age = 36.5 years (range 22–43)	3 months	Not reported	Not reported	44±23%[g]
(Vonck et al 2004) *Possible overlap of patients with Boon et al*	Level IV case series Quality assessment: Fair	118 patients with medically refractory epilepsy who were not suitable candidates for	Mean = 33 months (range 6–94)	29 (range 1–450)	Not reported	55±31.6% (range 0–100)

Study	Study design and quality appraisal	Population	Follow-up period	Absolute seizure frequency (seizures per month) Mean±SD		
				Baseline	Follow-up	Mean percentage change[a]
(2001) and Boon et al (2002)		resective surgery Mean age = 32 years (range 4–59)				

[a] Change in seizure frequency = (seizures per month during follow-up – seizures per month at baseline / seizures per month at baseline) x 100; [b] Wilcoxon's signed rank test; [c] Wilcoxon matched pairs test; [d] p value not reported; [e] severity of seizures was not reported for one subject; [f] statistically significantly different from baseline according to author's calculations; [g] reported as the overall mean of the change from baseline for individual patient data; SD = standard deviation; NS = not statistically significant; sz = seizures; PE = partial epilepsy; IGE = idiopathic generalised epilepsy; SGE = symptomatic generalised epilepsy

Table 57 Change in seizure frequency following VNS therapy in children

Study	Study design and quality appraisal	Population	Follow-up period	Absolute seizure frequency (seizures per month) Mean±SD		
				Baseline	At end of follow-up	Mean percentage change[a]
Partial epilepsies						
(Zamponi et al 2002)	Level IV case series Quality assessment: Good	13 children with refractory symptomatic or cryptogenic partial epilepsy	Mean = 13.6 months (range 6–22)	Not reported	Not reported	3 months (n=13): 66±31%[d] 6 months (n=13): 65±30%[d] 12 months (n=8): 61±29%[d]
Generalised epilepsies						
(Majoie et al 2005)	Level IV case series Quality assessment: Good	19 children with childhood epilepsy resembling Lennox-Gastaut syndrome	24 months	170	3 months: 126 12 months: 126 18 months: 156 24 months: 133 p=0.03[b]	3 months: 26% 12 months: 26% 18 months: 8% 24 months: 22%
(Parker et al 1999)	Level IV case series Quality assessment: Good	16 consecutive children with cryptogenic epileptic encephalopathy refractory to AED therapy Mean age = 11±3 years	6, 12 and 24 months	53±76	Not reported	6 months: 8±42%[d] (NS) 12 months: 14±48%[d] (NS) 24 months: Median = 43%[d] (p<0.05)
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	Range 1–6 months	Not reported	Not reported	1 month (n=46): Median = 42% (range (–98)–63) p<0.0001[b] 3 months (n=43): Median = 58% p<0.0001[b] 6 months (n=24): Median = 58% p<0.0001[b]
(Hosain et al 2000)	Level IV case series Quality assessment: Fair	13 patients with Lennox-Gastaut syndrome Median age = 13 years (range 4–44	6 months	65±39	29±30	56±26%[d] p=0.04[c]
Partial and generalised seizures						

Study	Study design and quality appraisal	Population	Follow-up period	Absolute seizure frequency (seizures per month) Mean±SD		
				Baseline	At end of follow-up	Mean percentage change[a]
(Koo 2001)	Level IV case series Quality assessment: Good	12 patients with medically refractive idiopathic generalised epilepsy Mean age = 14.1±7.0 years (range 4–31)	Mean = 16.8 months (range 12–23)	356±974 (range 5–4,488)	Not reported	3 months: 63±32% 6 months: 68±31% 12 months: 77±25%
(Hallbook et al 2005b) (Hallbook et al 2005a)	Level IV case series Quality assessment: Fair	15 paediatric patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	9 months	Median = 51 (range 2–200)	3 months: Median = 18 (range 2–141) 9 months: Median = 19 (range 0–112)	3 months: 65%, p<0.05[b] 9 months: 63%, p<0.05[b]
(Lundgren et al 1998a)	Level IV case series Quality assessment: Fair	16 children with intractable epilepsy who had failed intracranial surgery or who were not suitable candidates	Range 12–24 months	127±289	4–6 months: 62±82 (n=16) 10–12 months: 43±39 (n=16) 16–18 months: 55±56 (n=11) 22–24 months: 21±8 (n=2)	4–6 months: 20±50%[d] (n=16) 10–12 months: 26±55%[d] (n=16) (p>0.05) 16–18 months: 19±85%[d] (n=11) 22–24 months: 32±50%[d] (n=2)
(Patwardhan et al 2000)	Level IV case series Quality assessment: Fair	38 consecutive paediatric patients with medically refractive epilepsy *Note: Some of these patients were younger than 2 years old*	Median = 12 months (range 10–18)	Not reported	Not reported	66%
(Saneto et al 2006) *Some subjects are also included in study by Arthur et al (2007)*	Level IV case series Quality assessment: Fair	63 children aged less than 12 years, implanted with VNS. 43 subjects provided data relating to effectiveness outcomes.	6–18 months Mean = 18 months	Not reported	Not reported	<12 months: Median = 33% (n=5) 12–17 months: Median = 55% (n=16) ≥18 months: Median = 42% (n=22)

Study	Study design and quality appraisal	Population	Follow-up period	Absolute seizure frequency (seizures per month) Mean±SD		
				Baseline	At end of follow-up	Mean percentage change[a]
						Overall: Median = 84% (n=43)
(Alexopoulos et al 2006)	Level IV case series Quality assessment: Poor	46 paediatric patients with medically refractory epilepsy who had failed previous resective surgery or were not suitable candidates ≤12 years: n=21 >12 years: n=25	Median = 2 years	Not reported	Not reported	3 months: (Median) 56% (n=46) 6 months: 50% (n=45) 12 months: 63% (n=39) 24 months: 83% (n=23) 36 months: 74% (n=16)

[a] Change in seizure frequency = (100 – seizures per month during follow-up / seizures per month at baseline) x 100; [b] Wilcoxon's signed rank test; [c] Wilcoxon matched pairs test; [d] reported as the overall mean of the change from baseline for individual patient data; SD = standard deviation; sz = seizures

Table 58 Number of patients with 50% or 75% reduction in seizure frequency and/or severity following VNS implantation in adults

Study	Study design and quality appraisal	Population	Follow-up period	Number of patients with a reduction in seizure frequency following VNS implantation	
				≥50% reduction	≥75% reduction
Partial epilepsies					
(Marrosu et al 2005)	Level III-2 non-randomised, comparative study Quality assessment: Fair	21 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery *VNS group:* n=11 *Comparator:* AED therapy (n=10)	12 months	*VNS* 3/11 (27%) *AED therapy* 8/10 (80%) RR = 0.34 [95% CI: 0.12, 0.94] ARR = 0.53 [95% CI: 0.10, 0.75]	*VNS* 3/11 (27%) *AED therapy* 4/10 (40%) RR = 0.68 [95% CI: 0.20, 2.31] ARR = 0.13 [95% CI: –0.25, 0.46]
(Marrosu et al 2003)	Level III-2 non-randomised, comparative study Quality assessment: Fair	17 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery *VNS group:* n=10 *Comparator:* AED therapy (n=7)	12 months	*VNS* 4/10 (40%) *AED therapy* 0/7 (0%) RR = not definable ARR = –0.4 [95% CI: –0.69, 0.02]	*VNS* 4/10 (40%) *AED therapy* 0/7 (0%) RR = not definable ARR = –0.4 [95% CI: –0.69, 0.02]
(Alsaadi et al 2001)	Level IV case series Quality assessment: Good	10 adult patients with bilateral independent temporal lobe epilepsy. Patients were medically refractory and had failed intracranial surgery or were not considered suitable candidates	12 months	3 months: 3/10 (30%) 6 months: 6/10 (60%) 12 months: 6/10 (60%)	Outcome not reported
(Chavel et al 2003)	Level IV case series Quality assessment: Good	29 patients with medically refractory partial onset seizures	12–24 months	12 months (n=25): 54% 24 months (n=23): 61%, p<0.005	Outcome not reported
(Clarke et al 1997)	Level IV case series Quality assessment: Good	10 adult subjects with medically refractory complex partial epilepsy who were not suitable	50 months	5/9 (56%)	3/9 (33%)

Study	Study design and quality appraisal	Population	Follow-up period	Number of patients with a reduction in seizure frequency following VNS implantation	
				≥50% reduction	≥75% reduction
		candidates for intracranial surgery			
(Fai et al 2004)	Level IV case series Quality assessment: Good	13 Chinese patients with medically refractory partial-onset seizures Mean age = 25 years (range 13–40)	Mean = 47±18 months	3 months: 4/13 (31%) 12 months: 8/13 (62%) 18 months: 5/13 (38%)	3 months: 3/13 (23%) 12 months: 4/13 (31%) 18 months: 2/13 (15%)
(Uthman et al 1993) (Penry & Dean 1990) (Uthman et al 1990)	Level IV case series Quality assessment: Good	15 patients with medically refractory partial seizures EO1 study (n=11) EO2 study (n=4)	Mean = 25 months (range 14–36)	5/14 (36%)	Outcome not reported
(Ardesch et al 2007b)	Level IV case series Quality assessment: Fair	19 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Up to 6 years	1 year: 12% (n=19) 2 year: 33% (n=25) 3 year: 31% (n=16) 4 year: 36% (n=15) 5 year: 38% (n=9) 6 year: 25% (n=7)	Outcome not reported
(Kawai et al 2002)	Level IV case series Quality assessment: Fair	15 patients with medically refractory partial epilepsy who had failed resective surgery or were not suitable	Median = 56 months (range 48–91)	1 year (n=13): 6/13 (46%) 2 year (n=13): 7/13 (54%) 3 year (n=13): 10/13 (77%) 4 year (n=13): 9/13 (69%) 5 year (n=6): 5/6 (83%) 6 year (n=5): 3/5 (60%) 7 year (n=2): 1/2 (50%)	1 year (n=13): 1/13 (8%) 2 year (n=13): 4/13 (31%) 3 year (n=13): 4/13 (31%) 4 year (n=13): 7/13 (54%) 5 year (n=6): 4/6 (67%) 6 year (n=5): 2/5 (40%) 7 year (n=2): 0/2 (0%)
(Koutroumanidis et al 2003)	Level IV case series Quality assessment: Fair	16 patients with medically refractory complex partial epilepsy and who had failed previous resective	Mean±SD = 14±9 months (range 3–36)	3/16 (19%)	1/16 (6%)

Study	Study design and quality appraisal	Population	Follow-up period	Number of patients with a reduction in seizure frequency following VNS implantation	
				≥50% reduction	≥75% reduction
		surgery Mean age±SD = 36 ±11.5 years (range 12–39)			
(Morrow et al 2000)	Level IV case series Quality assessment: Fair	10 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 32 years (range 16–54)	Mean = 18 months (range 12–36)	5/10 (50%)	Not reported
(Brazdil et al 2001)	Level IV case series Quality assessment: Poor	12 adult patients with medically refractory focal or multifocal epilepsy. Patients had been assessed and found to be unsuitable candidates for resective surgery	6 months	3/10 (50%)	1/10 (10%)
Generalised epilepsies					
(Holmes et al 2004)	Level IV case series Quality assessment: Good	16 patients with IGE or SGE aged 12 years or older	12–21 months	7/16 (44%)	5/16 (31%)
(Labar et al 1999)	Level IV case series Quality assessment: Good	24 patients with generalised epilepsy which was medically refractory	3 months	11/24 (46%)	Not reported
(Ko et al 1996)	Level IV case series Quality assessment: Fair	3 male patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	Mean±SD = 9±3 months	1/3 (33%)	0/3 (0%)
(Kostov et al 2007)	Level IV case series Quality assessment: Fair	12 patients with medically refractory idiopathic generalised epilepsy Mean age±SD = 31 ±14 years (range 11–48)	Mean = 23 months (range 9–54)	8/12 (67%)	4/12 (33%)

Study	Study design and quality appraisal	Population	Follow-up period	Number of patients with a reduction in seizure frequency following VNS implantation	
				≥50% reduction	≥75% reduction
(Labar et al 1998)	Level IV case series Quality assessment: Fair	5 adults with medically refractory mixed symptomatic generalised epilepsy. All patients had been diagnosed with Lennox-Gastaut syndrome and one patient also had complex partial seizures.	9 months	0/5 (0%)	2/5 (40%)
(Karceski 2001)	Level IV registry study Quality assessment: Poor	544 patients from VNS patient registry database who had Lennox-Gastaut syndrome and with or without a prior history of CC	3, 6, 12 and 18 months	3 months: 174/341 (51%) 6 months: 91/160 (57%) Note: data only available for patients without history of CC 12 months: 107/168 (64%) 18 months: Data unreliable	Unable to extract data
Partial and generalised epilepsies					
(McLachlan et al 2003)	Level IV case series Quality assessment: Good	27 consecutive patients with medically refractory epilepsy (localised or generalised) who had failed resective surgery or were unsuitable candidates for such surgery Mean age = 30 years (range 12–46)	12 months	5/27 (19%)	Unable to extract data
(Amar et al 2004)	Level IV case series Quality assessment: Fair	921 patients from the VNS patient registry who had been implanted with the VNS device Median age = 28 years (range 1–66)	Up to 24 months	12 months: 48% 24 months: 55%	12 months: 29% 24 months: 31%
(Ben-Menachem et al 1999)	Level IV case series Quality assessment: Fair	64 patients with medically refractory epilepsy who had failed resective	Mean = 20 months (range 3–64)	Overall: 29/64 (45%) PE: 19/47 (40%) PGS:	PE: 8/47 (17%) PGS: 4/9 (44%) LGS:

Study	Study design and quality appraisal	Population	Follow-up period	Number of patients with a reduction in seizure frequency following VNS implantation	
				≥50% reduction	**≥75% reduction**
		surgery or who were not suitable candidates		5/9 (56%) LGS: 5/8 (63%)	Not reported
(Boon et al 2001b) *Overlap of patients with Boon et al (2002)*	Level IV case series Quality assessment: Fair	35 patients with partial seizures or Lennox-Gastaut syndrome who were refractory to AEDs and unsuitable candidates for resective surgery	Mean±SD = 35 months (range 9–73)	24/35 (69%)	11/35 (31%)
(Casazza et al 2006)	Level IV case series Quality assessment: Fair	17 adult patients with medically refractory epilepsy who had previously failed resective surgery or who were not suitable candidates	Range 4–9 years	4/17 (24%)	0/17 (0%)
(Chayasirisobhon et al 2003)	Level IV case series Quality assessment: Fair	34 patients with medically refractory epilepsy who were unsuitable for resective surgery Mean age = 27.6 years (range 5–70)	6 months	22/34 (65%) Children (≤12 years): 7/9 (78%)	13/34 (38%)
(De Herdt et al 2007) *Possibly some overlap of patients with Boon et al (2001) and Boon et al (2002)*	Level IV case series Quality assessment: Fair	138 consecutive patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 30±13 years (range 4–59)	Mean = 44±27 months (range 12–120 months)	Overall: 59% Children v adults: 43% v 62% PE v SGE: 59% v 57%	Not reported
(Tanganelli et al 2002)	Level IV case series Quality assessment: Fair	47 patients with medically refractory epilepsy without indication for resective surgery	Mean = 26 months (range 6–50)	22/47 (47%)	6/47 (13%)
(Andriola & Vitale 2001)	Level IV case series Quality	21 patients with developmental disability or mental	Range = 6 months – 3 years	11/16 (69%)	Not reported

Study	Study design and quality appraisal	Population	Follow-up period	Number of patients with a reduction in seizure frequency following VNS implantation	
				≥50% reduction	≥75% reduction
	assessment: Poor	retardation. Patients had medically refractive epilepsy and were not suitable candidates for resective surgery. Age range = 3–56 years			

RR = relative risk; CI = confidence intervals; ARR = absolute risk reduction; CC = corpus callosotomy; PE = partial epilepsy; SD = standard deviation; IGE = idiopathic generalised epilepsy; SGE = symptomatic generalised epilepsy; PGS = primary generalised seizures; LGS = Lennox-Gastaut syndrome

Table 59 Number of patients with 50% or 75% reduction in seizure frequency and/or severity following VNS implantation in children

Study	Study design and quality appraisal	Population	Follow-up period	Number of patients with a reduction in seizure frequency following VNS implantation	
				≥50 % reduction	≥75% reduction
Partial epilepsies					
(Zamponi et al 2002)	Level IV case series Quality assessment: Good	13 children with refractory symptomatic or cryptogenic partial epilepsy	Mean = 13.6 months (range 6–22)	3 months (n=13): 10/13 (78%) 6 months (n=13): 11/13 (85%) 12 months (n=8): 6/8 (75%)	3 months (n=13): 6/13 (46%) 6 months (n=13): 7/13 (54%) 12 months (n=8): 3/8 (38%)
Generalised epilepsies					
(Majoie et al 2005)	Level IV case series Quality assessment: Good	19 children with epilepsy resembling Lennox-Gastaut syndrome	24 months	4/19 (21%)	1/19 (5%)
(Parker et al 1999)	Level IV case series Quality assessment: Good	16 consecutive children with cryptogenic epileptic encephalopathy refractory to AED therapy Mean age = 11±3 years	6, 12 and 24 months	6 months: 2/16 (13%) 12 months: 4/16 (25%) 24 months: Not reported	6 months: 0/16 (0%) 12 months: 2/16 (13%) 24 months: Not reported
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	Range, 1-6 months	1 month (n=46): 20/46 (43%) 3 months (n=43): 24/43 (55%) 6 months (n=24): 15/24 (63%)	1 month (n=46): 7/46 (15%) 3 months (n=43): 15/43 (35%) 6 months (n=24): 9/24 (38%)
(Hosain et al 2000)	Level IV case series Quality assessment: Fair	13 patients with Lennox-Gastaut syndrome Median age = 13 years (range 4–44)	6 months	6/13 (46%)	5/13 (38%)
Partial and generalised epilepsies					
(Arthur et al 2007) *Majority of patients are also reported in Saneto et al (2006)*	Level IV case series Quality assessment: Fair	5 children with definite mitochondrial disease according to modified Walker criteria (Bernier et al 2002)	12–48 months	0/5 (0%)	Outcome not reported
(Chayasirisobhon et al 2003)	Level IV case series Quality assessment: Fair	34 patients with medically refractory epilepsy who were unsuitable for resective surgery Mean age =	6 months	Children (≤12 years): 7/9 (78%)	Not reported

Study	Study design and quality appraisal	Population	Follow-up period	Number of patients with a reduction in seizure frequency following VNS implantation	
				≥50 % reduction	≥75% reduction
		27.6 years (range 5–70)			
(Hallbook et al 2005b)	Level IV case series Quality assessment: Fair	15 paediatric patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	9 months	6/15 (40%)	1/15 (7%)
(Lundgren et al 1998a)	Level IV case series Quality assessment: Fair	16 children with intractable epilepsy who had failed intracranial surgery or were not suitable candidates	Range 12–24 months	4–6 months: 5/16 (31%) 10–12 months: 3/16 (19%)	4–6 months: 6/16 (38%) 10–12 months: 3/16 (19%)
(Nagarajan et al 2002)	Level IV case series Quality assessment: Fair	16 children with medically refractory epilepsy who were unsuitable candidates for intracranial surgery	Up to 47 months	10/16 (63%)	9/16 (56%)
(Patwardhan et al 2000)	Level IV case series Quality assessment: Fair	38 consecutive paediatric patients with medically refractory epilepsy *Note: Some of these patients were younger than 2 years old*	Median = 12 months (range 10–18)	26/38 (68%)	Not reported
(Saneto et al 2006) *Some subjects are also included in study by Arthur et al (2007)*	Level IV case series Quality assessment: Fair	63 children aged less than 12 years, implanted with VNS. 43 subjects provided data relating to effectiveness outcomes.	6–18 months	22/43 (51%)	20/43 (47%)
(You et al 2007) (Kang et al 2006)	Level IV case series Quality assessment: Fair	28 paediatric patients with medically refractory epilepsy. All patients had either multifocal or generalised epilepsy and	Mean±SD = 31.4±19.4 months (range 12 months – 7.7 years)	Overall: 15/28 (54%) Generalised epilepsies: 8/17 (47%) Partial epilepsies: 7/11 (64%)	Overall: 9/28 (32%) Generalised epilepsies: Not reported Partial epilepsies: Not reported

Study	Study design and quality appraisal	Population	Follow-up period	Number of patients with a reduction in seizure frequency following VNS implantation	
				≥50 % reduction	**≥75% reduction**
		were therefore unsuitable candidates for resective surgery			
(Alexopoulos et al 2006)	Level IV case series Quality assessment: Poor	46 paediatric patients with medically refractory epilepsy who had failed previous resective surgery or were not suitable candidates ≤12 years: n=21 >12 years: n=25	Median = 2 years	At last follow-up: 27/46 (59%)	At last follow-up: 20/46 (43%)

SD = standard deviation

Table 60 Continuation rate of VNS device in adults

Study	Study design and quality appraisal	Population	Follow-up period	Number receiving VNS therapy at end of follow-up (%)
Partial epilepsies				
(Marrosu et al 2003)	Level III-2 non-randomised, comparative study Quality assessment: Fair	17 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery *VNS group:* n=10 *Comparator:* AED therapy (n=7)	12 months	*VNS* 10/10 (100%) *AED therapy* 7/7 (100%)
(Ardesch et al 2007b)	Level IV case series Quality assessment: Fair	19 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery	Up to 6 years	16/19 (84%)
(Chavel et al 2003)	Level IV case series Quality assessment: Good	29 patient with medically refractory partial onset seizures	12–24 months	23/29 (79%)
(Kawai et al 2002)	Level IV case series Quality assessment: Fair	15 patients with medically refractory partial epilepsy who had failed resective surgery or were not suitable candidates	Median = 56 months (range 48–91)	10/13 (77%)
(Fai et al 2004)	Level IV case series Quality assessment: Good	13 Chinese patients with medically refractory partial-onset seizures Mean age = 25 years (range 13–40)	Mean = 47±18 months	8/13 (62%)
(Alsaadi et al 2001)	Level IV case series Quality assessment: Good	10 adult patients with bilateral independent temporal lobe epilepsy. Patients were medically refractory and had failed intracranial surgery or were not considered suitable candidates	12 months	9/10 (90%)
(Uthman et al 1993) (Penry & Dean	Level IV case series Quality	15 patients with medically refractory partial	Mean = 25 months (range 14–36)	14/15 (93%)

Study	Study design and quality appraisal	Population	Follow-up period	Number receiving VNS therapy at end of follow-up (%)
1990) (Uthman et al 1990)	assessment: Good	seizures EO1 study (n=11) EO2 study (n=4)		
(Hsiang et al 1998)	Level IV case series Quality assessment: Fair	6 Chinese patients with medically refractory partial epilepsy who were unsuitable candidates for resective surgery or had previously failed such surgery	Mean±SD = 15±4 months	6/6 (100%)
(Ko et al 1996)	Level IV case series Quality assessment: Fair	3 male patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	Mean±SD = 9±3 months	3/3 (100%)
(Koutroumanidis et al 2003)	Level IV case series Quality assessment: Fair	16 patients with medically refractory complex partial epilepsy who had failed previous resective surgery Mean age ± SD = 36 ±11.5 years (range 12–39)	Mean±SD = 14±9 months (range 3–36)	15/16 (94%)
(Morrow et al 2000)	Level IV case series Quality assessment: Fair	10 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 32 years (range 16–54)	Mean = 18 months (range 12–36)	9/10 (90%)
Generalised epilepsies				
(Holmes et al 2004)	Level IV case series Quality assessment: Good	16 patients with IGE or SGE aged 12 years or older	12–21 months	16/16 (100%)
(Labar et al 1999)	Level IV case series Quality assessment: Good	24 patients with generalised epilepsy which was medically refractory	3 months	24/24 (100%)
(Kostov et al 2007)	Level IV case series Quality	12 patients with medically refractive	Mean = 23 months (range 9–54)	12/12 (100%)

Study	Study design and quality appraisal	Population	Follow-up period	Number receiving VNS therapy at end of follow-up (%)
	assessment: Fair	idiopathic generalised epilepsy Mean age±SD = 31 ±14 years (range 11–48)		
(Labar et al 1998)	Level IV case series Quality assessment: Fair	5 adults with medically refractive mixed symptomatic generalised epilepsy. All patients had been diagnosed with Lennox-Gastaut syndrome and one patient also had complex partial seizures.	9 months	4/5 (80%)
Partial and generalised epilepsies				
(McLachlan et al 2003)	Level IV case series Quality assessment: Good	27 consecutive patients with medically refractory epilepsy (localised or generalised) who had failed resective surgery or were unsuitable candidates for such surgery Mean age = 30 years (range 12–46)	12 months	26/27 (96%)
(Smyth et al 2003)	Level IV retrospective case series Quality assessment: Good	74 consecutive paediatric patients with medically refractory multifocal or generalised epilepsy	Mean = 2.2 years	66/74 (89%)
(Ben-Menachem et al 1999)	Level IV case series Quality assessment: Fair	64 patients with medically refractory epilepsy who had failed resective surgery or were not suitable candidates for resective surgery	Mean = 20 months (range 3–64)	53/64 (83%)
(Boon et al 2001b) *Overlap of patients with Boon et al (2002)*	Level IV case series Quality assessment: Fair	35 patients with partial seizures or Lennox-Gastaut syndrome who were refractory	Mean±SD = 35 months (range 9–73)	35/35 (100%)

Study	Study design and quality appraisal	Population	Follow-up period	Number receiving VNS therapy at end of follow-up (%)
		to AEDs and unsuitable candidates for resective surgery		
(Casazza et al 2006)	Level IV case series Quality assessment: Fair	17 adult patients with medically retractable epilepsy who had previously failed resective surgery or were not suitable candidates 16 patients with drop attacks	Range 4–9 years	5/17 (29%)
(Chayasirisobhon et al 2003)	Level IV case series Quality assessment: Fair	34 patients with medically refractory epilepsy who were unsuitable for resective surgery Mean age = 27.6 years (range 5–70)	6 months	34/34 (100%)
(Lundgren et al 1998a)	Level IV case series Quality assessment: Fair	16 children with intractable epilepsy who had failed intracranial surgery or were not suitable candidates	Range 12–24 months National Hospital Seizure Severity Scale (NHS_3)	11/16 (69%)
(Rizzo et al 2003)	Level IV case series Quality assessment: Fair	10 patients with refractory generalised or partial epilepsy Median age = 36.5 years (range 22–43)	3 months	10/10 (100%)
(Tanganelli et al 2002)	Level IV case series Quality assessment: Fair	47 patients with medically refractory epilepsy without indication for resective surgery	Mean = 26 months (range 6–50)	45/47 (96%)
(Vonck et al 2004) *Possible overlap with Boon et al (2001) and Boon et al (2002)*	Level IV case series Quality assessment: Fair	118 patients with medically refractory epilepsy who were not suitable candidates for resective surgery Mean age = 32 years (range 4–59)	Mean = 33 months (range 6–94)	112/118 (95%)
(Alexopoulos et al 2006)	Level IV case series Quality	46 paediatric patients with medically refractory	Median = 2 years	Overall = 37/6 (80%)

Study	Study design and quality appraisal	Population	Follow-up period	Number receiving VNS therapy at end of follow-up (%)
	assessment: Poor	epilepsy who had failed previous resective surgery or were not suitable candidates ≤12 years: n=21 >12 years: n=25		
(Andriola & Vitale 2001)	Level IV case series Quality assessment: Poor	21 patients with developmental disability or mental retardation. Patients had medically refractory epilepsy and were not suitable candidates for resective surgery.	Range = 6 months – 3 years	20/21 (95%)
(Blount et al 2006)	Level IV case series Quality assessment: Poor	7 patients with medically refractory, multifocal, catastrophic epilepsy	Mean = 21±20 months	6/7 (86%)

SD = standard deviation; IGE = idiopathic generalised epilepsy; SGE = symptomatic generalised epilepsy

Table 61 Continuation rate of VNS device in children

Study	Study design and quality appraisal	Population	Follow-up period	Number receiving VNS therapy at end of follow-up (%)
Partial epilepsies				
(Rychlicki et al 2006) (Zamponi et al 2002)	Level IV case series Quality assessment: Good	36 children with refractory symptomatic or cryptogenic partial epilepsy	Mean = 31 months (range 3–52)	35/36 (97%)
Generalised epilepsies				
(Majoie et al 2005)	Level IV case series Quality assessment: Good	19 children with epilepsy resembling Lennox-Gastaut syndrome	24 months	18/19 (95%)
(Parker et al 1999)	Level IV case series Quality assessment: Good	16 consecutive children with cryptogenic epileptic encephalopathy refractory to AED therapy Mean age = 11±3 years	6, 12 and 24 months	15/16 (94%)
(Frost et al 2001)	Level IV retrospective case series Quality assessment: Fair	50 patients with Lennox-Gastaut syndrome Median age = 13 years (range 5–27)	Range 1–6 months	50/50 (100%)
(Hosain et al 2000)	Level IV case series Quality assessment: Fair	13 patients with Lennox-Gastaut syndrome Median age = 13 years (range 4–44)	6 months	13/13 (100%)
Partial and generalised epilepsies				
(Nagarajan et al 2002)	Level IV case series Quality assessment: Fair	16 children with medically refractory epilepsy who were unsuitable candidates for intracranial surgery	Up to 47 months	15/16 (94%)
(Patwardhan et al 2000)	Level IV case series Quality assessment: Fair	38 consecutive paediatric patients with medically refractory epilepsy *Note: Some of these patients were younger than 2 years old*	Median = 12 months (range 10–18)	37/38 (97%)
(Saneto et al 2006) *Some subjects*	Level IV case series Quality	63 children aged less than 12 years	6–18 months Mean = 18 months	43/43 (100%)

Study	Study design and quality appraisal	Population	Follow-up period	Number receiving VNS therapy at end of follow-up (%)
are also included in study by Arthur et al (2007)	assessment: Fair	implanted with VNS. 43 subjects provided data relating to effectiveness outcomes.		
(You et al 2007) (Kang et al 2006)	Level IV case series Quality assessment: Fair	28 paediatric patients with medically refractory epilepsy. All patients had either multifocal or generalised epilepsy and were therefore unsuitable candidates for resective surgery	Mean±SD = 31.4±19.4 months (range 12 months – 7.7 years)	28/28 (100%)
(Hallbook et al 2005b) (Hallbook et al 2005a)	Level IV case series Quality assessment: Fair	15 paediatric patients with medically refractory epilepsy who had failed intracranial surgery or were not suitable candidates	9 months	14/15 (93%)
(Lundgren et al 1998a)	Level IV case series Quality assessment: Fair	16 children with intractable epilepsy who had failed intracranial surgery or were not suitable candidates	Range 1–24 months	16/16 (100%)
(Alexopoulos et al 2006)	Level IV case series Quality assessment: Poor	46 paediatric patients with medically refractory epilepsy who had failed previous resective surgery or were not suitable candidates ≤12 years: n=21 >12 years: n=25	Median = 2 years	33/46 (72%)
(Buoni et al 2004a)	Level IV case series Quality assessment: Poor	13 patients with medically refractory epilepsy who were unsuitable candidates for resective surgery Mean age = 17 years (range 6–28)	Mean = 22 months (range 8–36)	12/13 (92%)

Appendix G Excluded studies

Incorrect intervention

Kossoff, E.H., Pyzik, P.L. et al (2007). 'Combined ketogenic diet and vagus nerve stimulation: rational polytherapy?' *Epilepsia,* 48 (1), 77–81.

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Glossary and abbreviations

AED	Anti-epileptic drug
AIHW	Australian Institute of Health and Welfare
Agranulocytosis	A serious condition in which the bone marrow fails to produce white blood cells
Anorexia	Lack of appetite
Aplastic anaemia	Where the bone marrow fails to produce blood cells
Aspiration	Inhalation of material (particularly food and liquid) into the airway and lungs
Ataxia	Loss of muscle coordination
Aura	A sensation or warning before a seizure occurs
Automatisms	Abnormal body movements which occur during some epileptic seizures
Bradycardia	Abnormally slow heart rate
Cryptogenic	Referring to a disease with no identifiable cause
CT	Computed tomography—a specialised non-invasive procedure using X-rays to provide computerised images of the body
Dysautonomia	Dysfunction of the autonomic nervous system (eg heart rate, breathing, sweating and salivation)
Dysmnestic	The perception of memory is altered in dysmnestic seizures. Two types of dysmnestic seizures are commonly reported. Déjà vu is the false impression of life repeating itself. Jamais vu is the false impression that familiar objects, persons or situations have not been encountered before.
Dyspepsia	Indigestion
Dysphagia	Difficulty in swallowing
EEG	Electroencephalogram—a recording of the brain's continuous electrical activity using electrodes attached to the scalp
Emesis	Vomiting

Epileptiform	Resembling epilepsy, can refer to patterns seen on EEG
FDG-PET	Positron emission tomography which uses glucose analogue [18 F] fluorodeoxyglucose
Hypohidrosis	Decreased ability to perspire or sweat
Hyponatraemia	A deficiency of sodium in the blood
Ictal	The seizure event
Idiopathic	Without a known cause
Inspiratory stridor	A high-pitched sound heard during inspiration
Interictal	Period between seizures
LGS	Lennox-Gastaut syndrome—an epileptic syndrome of intractable epilepsy which generally manifests between the ages of 2 and 6 years. Often characterised by mental retardation, and slow spike and wave on the electroencephalogram. Multiple seizure types often occur, particularly atypical absence, tonic and atonic.
Lymphadenopathy	Disease or swelling of the lymph nodes
MBS	Medicare Benefits Schedule
Monotherapy	Treatment with a single anti-epileptic drug
MRI	Magnetic resonance imaging—a non-invasive, non X-ray imaging technique using magnetic fields. Particularly useful for imaging soft tissues
MSAC	Medical Services Advisory Committee
NCP	NeuroCybernetic Prosthesis
Nephrolithiasis	Kidney stones
Occipital	Pertaining to the back of the head or brain
Paraesthesia	A sensation of tingling or numbness
PET	Positron emission tomography—an imaging scan that measures metabolic activity in the brain by measuring its use of glucose. Useful in planning intracranial surgery.
Pharyngodynia	Pain in the pharynx, also called pharyngalgia

Polytherapy	The use of two or more anti-epileptic drugs
Pruritus	Itching skin
Somnolence	An extreme form of drowsiness
SPECT	Single photon emission computed tomography—a special type of CT scan which measures blood flow in the brain
Status epilepticus	Repeated seizures or a seizure prolonged for at least 30 minutes—a condition which is severe and potentially life-threatening but not always related to epilepsy. Status epilepticus can result from acute brain injury.
Sternocleidomastoid muscle	Anterior muscles in the neck which aid in flexing and rotating the head
Stevens-Johnson syndrome	A severe and life-threatening condition characterised by fever and flu-like symptoms followed by a severe, blistering rash on the skin and/or mucous membranes
SUDEP	Sudden unexpected death in epilepsy. Death which occurs without an apparent cause but which is presumed to be related to the person's epilepsy.
Symptomatic	Referring to a disorder with an identifiable cause
Tachycardia	Abnormally fast heart rate
Temporal	Lateral region of the head
TGA	Therapeutic Goods Administration
Torticollis	Muscle spasms, usually in the neck, which result in an abnormal head position
VNS	Vagus nerve stimulation—therapy which provides repeated electrical stimulation to the left vagus nerve with the aim of preventing seizures

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