NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of vagus nerve stimulation for treatment-resistant depression

Depression is associated with feelings of sadness, despair, helplessness, hopelessness and lack of interest in life. People with severe depression may be unable to eat or sleep or to take part in social activities, and may become completely withdrawn. Vagus nerve stimulation aims to improve mood regulation and reduce depression by stimulating the nerve in the neck that carries signals to the brain areas involved. A generator implanted under the skin in the chest area is used to provide electrical stimulation to the nerve.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in May 2009.

Procedure name

- Vagus nerve stimulation for treatment-resistant depression

Specialty societies

- British Psychological Society
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Psychiatrists
- Society of British Neurological Surgeons

Description

Indications and current treatment

Depression refers to a wide range of mental health problems characterised by loss of interest in and enjoyment of life, low mood and a range of associated emotional, cognitive, physical and behavioural symptoms. Behavioural and physical symptoms typically include tearfulness, irritability, social withdrawal, reduced sleep, decreased appetite, lack of libido, fatigue and diminished activity. Low self-esteem and loss of confidence are common, as are feelings of guilt and worthlessness. Some people with severe depression may also develop psychotic symptoms (hallucinations and/or delusions). In some people with depression, the condition co-exists with other mental health problems, such as anxiety. Some people have bipolar disorder, a disease characterised by different periods of depression, normal mood or mania. Depression is associated with risk of suicide attempt and suicide. The more severe the episode of depression, the less likely it is that remission will occur spontaneously.

At times, it can be difficult to distinguish the mood changes of depression from those that occur ‘normally’; diagnosis is usually based on persistence and severity of mood changes, the presence of other symptoms and the degree of functional and social impairment.

There are several scales used to measure depression severity. The Hamilton Depression Rating Scale (HDRS) usually uses a semi-structured interview to assess several variables (including depressed mood, insomnia, agitation, anxiety and weight loss) measured on five-point or three-point scales, with low values indicating less depression. Depending on the version of the scale used, scores of10 or less are often considered to represent remission. The inventory of depressive symptomology (IDS) is a 30-item questionnaire that gives scores ranging from 0 to 84 (low values represent less depression).

Conventional treatment for depression includes antidepressant medication, psychological therapies (including cognitive behavioural therapies) or a combination of both. Electroconvulsive therapy (ECT) is also sometimes used to treat depression that has proven resistant to other treatments. Electroconvulsive therapy involves the application of electrical current through the brain while the patient is under general anaesthesia, and muscle relaxants are used to minimise muscular contraction. Some patients may not respond to these treatments (refractory depression) or may relapse over time.

What the procedure involves

The procedure aims to improve mood regulation and reduce depression by stimulating the vagus nerve. It is licensed for use only after a number of courses of medical treatment have failed.

The insertion procedure is carried out with the patient under general or local anaesthesia. An incision is made in the left lateral aspect of the neck and the

left vagus nerve is identified. A stimulator electrode is cuffed around the nerve, tunneled subcutaneously to the left chest wall and attached to a pacemaker-like pulse generator which is implanted into a subcutaneous pocket.

The nerve is stimulated periodically (short period of stimulation follow by a few minutes rest), at a low intensity at first; the stimulation is then gradually increased via an external (remote) electronic control. Patients may temporarily inhibit stimulation by activating a switch with a magnet.

List of studies included in the overview

This overview is based on a maximum of 1855 patients from one systematic review[1], two randomised controlled trials[2,3] , one non-randomised controlled trial[7], and three case series[4,5,6]. It is possible that some patients have been reported more than once in these studies.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Efficacy

A systematic review including 1251 patients from 18 studies reported that response rate (defined as a 50% improvement over baseline HDRS score) after vagus nerve stimulation (VNS) in treatment-resistant depression ranged from 30.5% to 40% in 'short-term' studies (up to 10-week follow-up) and between 27% and 58% in 'long-term' studies (minimum 12-month follow-up)[1]. In the only randomised controlled trial included in the systematic review there was no significant difference in change in HDRS scores between the VNS group and the sham treatment group. However, there was a significant difference in favour of VNS in outcomes evaluated using the IDS scale ($p = 0.032$) (absolute figures and length of follow-up not reported).

A randomised controlled trial of 222 patients reported that 33% of patients with unipolar depressive symptoms and 38% of patients with depressive bipolar disease demonstrated a response (definition as above) at 24 months compared with baseline[3].

A randomised controlled trial of nine patients reported increased activity in the bilateral superior temporal gyrus and left somatosensory cortex, and significant decreases in activity in the left middle frontal gyrus, left fusiform gyrus, left ventromedial frontal lobe, right cerebellum and midbrain during VNS therapy. During sham therapy there were significant increases of activity in the right orbitofrontal cortex and the right parietal cortex, but no significant decreases in any area[2].

A case series of 264 patients reported that of 59 patients in a pilot study, 61% (11/18) who were early responders still had a response at 24-month follow-up. Regression analysis indicated that whether depression was refractory to medical treatment at baseline had a significant effect on whether patients

were responders or not ($p < 0.05$)[4]. The same study reported follow-up to 24 months of 205 patients; 77% (23/30) of patients who were early responders maintained a response to VNS treatment at late follow-up.

A case series of 74 patients reported that mean HDRS scores improved significantly compared with baseline at 12-month follow-up ($p < 0.0001$; absolute figures not reported) and that 55% of patients were responders at this time[5].

A case report of nine patients reported that no patients were responders at 1-week follow-up but by final follow-up (12 months or longer) 56% (5/9) of them were responders and 44% (4/9) were in remission[6].

A non-randomised controlled study of 18 patients reported that the there was a significantly greater decrease from baseline in the number of psychiatric consultations per year in the VNS group (33 ± 3.9 to 14 ± 2.2) than in the group of patients treated with medication and psychotherapy (24.0 ± 6.8 to 25.3 ± 8.1) at 12 months follow up ($p < 0.001$)[7].

Safety

A systematic review of 1251 patients from 18 studies reported serious or clinically important adverse events in 17% (10/59) of patients in one study[1]. This included two patients with worsening depression and one myocardial infarction. Hypomania or mania occurred in 2% (2/112) of patients after VNS. In six short-term studies two patients discontinued treatment or broke protocol because of adverse events and one patient committed suicide. The systematic review concluded that most long-term side effects are generally the same as those reported in short-term studies; they are typically mild and are limited to the time the stimulation is active.

A case series of 74 patients receiving VNS for depression that was refractory to treatment reported suicide in 2% of 61 patients available at 6-month follow-up , by 12 months follow up 2 suicides had occured[5]. At 3-month follow-up 1% of patients had a manic episode, 1% had worsening depression, 10% had dyspnoea and 20% reported pain (not otherwise defined). The most common adverse events were cough and voice alteration (26% and 63% of patients, respectively, at 3 months).

A case report of nine patients reported no major complications resulting from VNS implantation or in the postoperative period. 100% (9/9) of patients reported hoarseness but this decreased with time[6].

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to vagus nerve stimulation for severe depression. Searches were conducted of the following databases, covering the period from their commencement to 6th

May 2009 and updated to 28th August 2009: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy).

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with treatment-resistant depression
Intervention/test	Vagus nerve stimulation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

Existing assessments of this procedure

A Blue Cross/Blue Shield technology evaluation centre report (assessment program 21, no. 7) was published in August 2006. The report concluded that reviewed clinical trials reported weak evidence that did not demonstrate efficacy, and that the available evidence did not permit conclusions regarding the effect of VNS therapy on health outcomes or its effect compared with alternative therapies.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Vagus nerve stimulation for refractory epilepsy in children. NICE interventional procedures guidance 50 (2004). Available from www.nice.org.uk/IPG050

- Transcranial magnetic stimulation for severe depression. NICE interventional procedures guidance 242 (2007). Available from www.nice.org.uk/IPG242

Clinical Guidelines

- Depression: management of depression in primary and secondary care. NICE clinical guideline 23 (2007). Available from www.nice.org.uk/CG023

Table 2 Summary of key efficacy and safety findings on vagus nerve stimulation for treatment-resistant depression

Abbreviations used: ECT, electro-convulsive therapy; HDRS.,Hamilton depression rating scale; IDS, inventory of depressive symptomology ; TRD, treatment-resistant depression			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**

Abbreviations used: ECT, electro-convulsive therapy; HDRS.,Hamilton depression rating scale; IDS, inventory of depressive symptomology ; TRD, treatment-resistant depression

Study details	Key efficacy findings	Key safety findings	Comments
Daban C (2008)[1] **Systematic review** Spanish review of international studies Study period: Search dates Jan 2000 to Sept 2007 Study population: TRD n = **1251 (18 studies)** ***Short-term studies*** Rush (2000) n = 30 Sackeim (2001) n = 59 Armitage (2003) n = 7 Rush (2005) n = 222 (112 active VNS) O'Keane (2005) n = 11 Neuhaus (2007) n = 13 ***Long-term studies*** Marangell (2002) n = 30 Rush (2005a) n = 205 (95 active VNS) Nahas (2005) n = 59 George (2005) n = 329 (205 VNS) Conway (2005) n = 1 Martinez (2006) n = 1 Corcoran (2006) n = 11 Burke (2006) n = 205 Frick (2006) n = 60 Frick (2006a) n = 25 Critchley (2007) n = 1 Sperling (2007) n = 1	In all studies: • 'Response' was defined as more than a 50% reduction in baseline HDRS score at the end of the trial. • 'Remission' was defined as a HDRS total score of ≤ 10 at study endpoint. **Response** ***Short-term effects*** (up to 10-week follow-up) The only RCT. Rush (2005) reported no significant difference in change in HDRS score between VNS and sham. However, there was a significant difference in favour of VNS in IDS score ($p = 0.032$). Rush (2000) reported response in 40% of patients and remission in 17% after 10 weeks of treatment. Sackeim (2001) reported response in 30.5% of patients and remission in 15.3%. Armitage (2003) reported a significant improvement in HDRS score from baseline ($p < 0.0005$). 4 of 7 patients were responders, and 2 of 7 were in remission. O'Keane (2005) reported a significant decrease in HDRS and IDS score but only 1 of 11 patients was a responder. Neuhaus (2007) reported that almost 40% of patients were responders. ***Long-term effects*** (minimum 12-month follow-up) Marangell (2002) reported a response rate of 46% and a remission rate of 29% at 12 months (which was a significant improvement over 10-month follow-up, $p = 0.045$). Nahas (2005) reported a significant improvement in HDRS from 36.5 ± 5.8 points at baseline to 20.2 ± 11.2 points at 2-year follow-up ($p < 0.001$). George (2005) reported that 27% of patients receiving VNS were responders at 12 months compared with 13% of patients receiving treatment as usual ($p < 0.011$). Burke (2006) reported that there were comparable improvements in HDRS between patients receiving VNS plus ECT, and VNS alone. Frick (2006a) reported response in 58% of patients and remission in 36% at 1-year follow-up. Four case reports (Conway 2005; Critchley 2007; Martinez 2006; Sperling 2007) reported an ongoing antidepressant effect for up to 45 months.	**Complications** ***Short term*** Rush (2005) reported that 2% (2/112) of patients in the VNS group had significant hypomania or mania; one of these patients had bipolar disorder. These complications in both patients resolved within 2 weeks (additional treatment not reported). Sackeim (2001) reported serious or clinically important adverse events in 17% (10/59) of patients. Two patients had worsening depression and one had a myocardial infarction that may have been related to VNS. In the six short-term studies included, three patients discontinued the study because of adverse events, including one suicide. Symptoms reported frequently by patients relating to nerve stimulation included hoarseness, headache, sore throat and neck pain. ***Long term*** Rush (2005a) reported mania in 1% (3/205) of patients receiving VNS. Two other studies reported no significant changes regarding manic symptoms. Rush (2005a) reported that 15% (30/205) of patients had worsening depression requiring hospitalisation at 12-month follow-up. Most side effects were generally the same as those reported in the short-term studies. They were typically mild and limited to the time of the stimulation.	Inclusion criteria may have been different across included studies, similarly definition of treatment resistance. Searches limited to Medline, psychological abstracts and current contents. Inclusion criteria included prospective studies, current non-psychotic TRD and standard outcome measures. Of 98 studies identified 18 met the review criteria. No formal quality assessment of studies was undertaken. No assessment was made of possible publication bias. Only one RCT was identified which precluded meta analysis. In many included studies the patients had concomitant treatment; where medication was used the dose had to be stable for 4 weeks. Most included studies used a stimulation adjustment period.

Abbreviations used: ECT, electro-convulsive therapy; HDRS.,Hamilton depression rating scale; IDS, inventory of depressive symptomology ; TRD, treatment-resistant depression			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Daban (2008) continued. Inclusion criteria: not reported Technique: Vagus nerve stimulation. Usually at 0.25 mA, 500 microsecond pulse width and 20−30 Hz for 30 seconds on and 5 minutes off. But not otherwise defined. Follow-up: **not reported** Conflict of interest: Review supported by government grant.			Some double counting of patients, described where applicable.

Abbreviations used: ECT, electro-convulsive therapy; HDRS.,Hamilton depression rating scale; IDS, inventory of depressive symptomology ; TRD, treatment-resistant depression			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Nahas (2007)[2] **Randomised controlled trial** USA Study period: not reported Study population: TRD for at least 2 months but less than 6 months. Non-psychotic major depressive disorder (n = 14) or depressed phase bipolar disorder (n = 3). Age: 47 years (mean). Sex: 33% male n = **9 (crossover design vs sham)** Inclusion criteria: not reported Technique: VNS initiated 2 weeks after implantation, and with a 2-week intensity adjustment phase. Magnetic resonance imaging (MRI) brain scans undertaken to measure blood oxygenation level dependent (BOLD) signal during VNS and during sham treatment (placebo). Follow-up: **3 months** Conflict of interest: Supported by manufacturer.	**Brain imaging** From 45 scans during VNS significant increases in BOLD signal were observed in the bilateral superior temporal gyrus and left somatosensory cortex. Significant decreases in BOLD signal were seen in the left middle frontal gyrus, left fusiform gyrus, left ventromedial frontal lobe, right cerebellum and midbrain. From 9 scans during placebo (sham) treatment significant increases in BOLD signal were seen in the right orbitofrontal cortex and the right parietal cortex. No significant decreases were seen. **Association between depression symptoms and MRI BOLD findings** Multiple regression reported that the severity of depressive symptoms (HDRS) was associated with significant increases in BOLD signal in the right temporal lobe, right insula and left middle front gyrus ($p < 0.0001$, $r^2 = 0.76$). Other factors tested included time from first VNS activation, output current of VNS therapy and severity of illness.	Safety outcomes were not reported on.	Prospective study. Clinicians blinded to the treatment group undertook evaluation of HDRS before each brain scan.

Abbreviations used: ECT, electro-convulsive therapy; HDRS.,Hamilton depression rating scale; IDS, inventory of depressive symptomology ; TRD, treatment-resistant depression

Study details	Key efficacy findings	Key safety findings	Comments
Nierenberg A A (2008)[3] **Randomised controlled trial** USA Study period: Not reported Study population: Patients with diagnosed bipolar or unipolar depression. Age: not reported. Sex: not reported n = **222 (112 VNS vs sham)** Inclusion criteria: Chronic (> 2 years) or recurrent major depressive episode, baseline HDRS score ≥ 20 points, without rapid cycling bipolar disorder, and failure of between 2 and 6 mood disorder treatments. Technique: VNS not otherwise described vs sham treatment Follow-up: **3 months RCT and 2 years open label therapy** Conflict of interest: Supported by manufacturer.	**Medication use** At 12-month follow-up 56% (14/25) of patients with bipolar disorder were taking selective serotonin reuptake inhibitors, compared with 55% (116/210) of patients with unipolar disorder. **Quality of life** Median (range) group change from baseline to 12 months Unipolar (n = 94) Bipolar (n = 9) SF-36 Physical −2.05 −6.18 (−39.18 to 19.57) (−27.92 to 17.92) SF-36 Mental 8.39 10.54 (−19.20 to 40.23) (−3.42 to 35.45) Measurement of significance not reported. SF-36 = short form health survey. **Response** HDRS score change from baseline to 24 months < 0% 0% to 25% 25% to 50% 50% to 75% > 75% Unipolar 13% 31% 23% 24% 9% Bipolar 13% 25% 4% 19% 19% Measurement of significance not reported.	Safety outcomes were not reported on.	The same patients as in Rush (2005) included in the Daban (2008) study were included here but with longer outcomes reported. During the active phase of the study 52% of the patients with bipolar disorder and 50% of the unipolar patients were allotted to the VNS group, the others to sham therapy. By 24-month follow-up 28% of the bipolar patients and 25% of the unipolar patients had withdrawn from the study. The analysis did not report outcomes per treatment group, only comparing the outcomes for bipolar vs unipolar depressive patients who had been selected evenly across the two treatment arms. The total percentages for the HDRS response in the bipolar group did not add up to 100. It is likely that the 25% to 50% improvement figure should read 25%.

Abbreviations used: ECT, electro-convulsive therapy; HDRS.,Hamilton depression rating scale; IDS, inventory of depressive symptomology ; TRD, treatment-resistant depression

Study details	Key efficacy findings	Key safety findings	Comments
Sperling W (2009)[7] **Non randomised controlled trial** Germany Study period: 2000 to 2005 Study population: Patients with major depression and therapy resistant disease. Age:50 years (mean). Sex: 56% female n = **18 (9 VNS vs medication and psychotherapy)** Inclusion criteria: not repotred. Technique: VNS and 4 weeks of adjustment to individual response vs medication and psychotherapy Follow-up: **12 months (median)** Conflict of interest: not reported	**Response** Group Mean and Standard deviation HDRS score VNS / Medication / psychotherapy Baseline (n=18): 23.7 ± 2.4 / 23 ± 3* 12 months (n=18): 10.2 ± 2.4 / 22 ± 2* p= <0.001 / 0.095 Difference between groups (p<0.001) * derived from graphical figure, not reported in text **Psychiatric consultations** Group Mean and Standard deviation number of visits per year VNS / Medication / psychotherapy Baseline (n=18): 33 ± 3.9 / 24.9 ± 6.8 12 months (n=18): 14 ± 2.2 / 25.3 ± 8.1 p= <0.001 / Not reported Difference between groups (p<0.001) **Medication use** Group Mean and Standard deviation psychotropic drugs per day VNS / Medication / psychotherapy Baseline (n=18): 4.1 ± 0.8 / 3.4 ± 1.3 12 months (n=18): 2.7 ± 0.5 / 3.8 ± 1.9 p= <0.001 / NS (measurement of significance between groups not reported)	Safety outcomes were not reported on.	Follow up technique / schedule not reported No statistically significant differences between the groups at baseline in clinical or demographic characteristics

Abbreviations used: ECT, electro-convulsive therapy; HDRS.,Hamilton depression rating scale; IDS, inventory of depressive symptomology ; TRD, treatment-resistant depression			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Sackeim H A (2007)[4] **Cases series** USA Study period: not reported Study population: Patients with TRD. Age: 46 years. Sex: 28% male. HDRS = 29 points (mean) n = **264** Inclusion criteria: chronic or recurrent major depressive episode (unipolar or bipolar), HDRS > 18 points. Technique: VNS following 2 week recovery from implantation and 2 week adjustment period. Follow-up: **2 years** Conflict of interest: Supported by manufacturer.	**Response** <u>Pilot study n = 59 at baseline.</u> Using the 40% improvement in HDRS score criterion as the threshold for maintaining response, 72% (13/18) of early responders maintained benefit at 12-month follow-up and 61% (11/18) still maintained benefit at 24 months. 79% (11/14) of late responders maintained benefit at 24-month follow-up. From onset of response (not otherwise defined) until 24-month follow-up the mean improvement in HDRS score was 61.6 ± 20.6% in early responders, 60.8 ± 21.4% in the late responders and 24.5 ± 18.8% in the non-responders. Simultaneous logistic regression found that history of ECT treatment was not a predictor of response; however, resistance to medication at baseline had a significant effect on response ($p < 0.05$). <u>Pivotal study, n = 205 at baseline.</u> Using the 40% improvement in HDRS score criterion as the threshold for maintaining response, 63% (19/30) early responders maintained benefit at 12-month follow-up and 77% (23/30) still maintained benefit at 24 months. 65% (26/40) of late responders maintained benefit at 24-month follow-up. From onset of response (not otherwise defined) until 24-month follow-up the mean improvement in HDRS score was 54.7 ± 16.1% in early responders, 51.3 ± 20.5% in the late responders and 12.9 ± 19.0% in the non-responders.	No safety outcomes were reported on.	The same patients as in Sackeim (2001) included in the Daban (2008) study were included here but with longer outcomes reported. Response was defined as an improvement over baseline HDRS score of 50% for early response (3 months) or 40% for long-term follow-up (12 months). This series represents two groups of patients − one group in the pilot RCT study and one group in a 'pivotal' study. Patients in the pivotal study were allowed medication changes during treatment.

Abbreviations used: ECT, electro-convulsive therapy; HDRS.,Hamilton depression rating scale; IDS, inventory of depressive symptomology ; TRD, treatment-resistant depression

Study details	Key efficacy findings	Key safety findings	Comments
Schlaepfer T E (2008)[5] **Case series** European Study period: not reported Study population: Patients with TRD, non-psychotic major depressive disorder or bipolar disorder. Age: 47 years. Sex: 32% male. Unipolar = 73%, $HDRS_{24}$ = 29 points (mean), IDS = 47 points (mean) n = **74** Inclusion criteria: Depressive episode for >2 years or 4 previous episodes, patients without atypical or psychotic depression. Technique: VNS with implantable programmable pulse generator and helical electrodes wrapped around the vagus nerve. Following 2 week recovery from implantation, 2 week adjustment period with intensity of 0.25 mA, pulse width of 500 microseconds, and frequency of 20 Hz with stimulation set at 30 seconds on and 5 minutes off. Stimulation increased at 0.25 mA increments. Follow-up: **12 months** Conflict of interest: Supported by manufacturer.	**Response** Patients were considered as responders if they had a reduction in HDRS score of more than 50% from baseline. The percentage of patients that were responders was 36% (25/70) at 3 months, 44% (27/61) at 6 months, 53% (29/55) at 9 months and 55%(33/60) at 12 months. Mean HRDS score improved significantly from baseline at all follow-up periods to 12 months ($p < 0.0001$) (absolute figures not reported). The mean IDS score fell significantly from baseline to 12-month follow-up by 41% ($p < 0.0001$).	**Complications** 3 months (n = 70) / 6 months (n = 61) Suicide 0% / 2% Manic reaction 1% / 0% Worsening depression 1% / 0% Paraesthesia 1% / 0% Dyspnoea 10% / 5% Dysphagia 6% / 0% Pruritus 4% / 0% Pharyngitis 6% / 3% Pain 20% / 0% Headache 3% / 2% 'Increased cough' (not defined) 26% / 3% Voice alteration 63% / 2% Absolute figures not reported At 1-year follow-up there were 15 adverse events requiring hospitalisation: 7 episodes of worsening depression, two suicides, one brain haemorrhage due to attempted suicide, one nephrolithiasis, one cholelithiasis, one pulmonary embolism, one episode of mania and one episode of syncope. Of these only the manic episode was judged by the investigator to be related to stimulation.	9 participating centres. Open label prospective uncontrolled trial. Concomitant antidepressant medication was allowed but had to be stable for 4 weeks before baseline measurements were made. During the long-term follow-up (after 3 months) changes in stimulation parameters and medication were permitted. Of 74 patients implanted with VNS 5% (4/74) discontinued in the acute phase (up to 3 months) and 10% (7/74) withdrew during follow-up. 5 patients withdrew because of lack of efficacy, and 2 patients committed suicide.

Abbreviations used: ECT, electro-convulsive therapy; HDRS.,Hamilton depression rating scale; IDS, inventory of depressive symptomology ; TRD, treatment-resistant depression			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Franzini A (2008)[6] **Cases report** Italy Study period: Jan 2000 to Nov 2006 Study population: Patients with TRD. Age: 43 to 80 years (range). Sex: 56% male. n = **9** Inclusion criteria: Depressive episode for > 2 years, patients without atypical or psychotic depression or Schizoaffective disorder. Failed > 4 antidepressant medication trials, and 6 months of psychotherapy. Technique: General anaesthesia VNS with implantable pulse generator and coil shaped electrodes wrapped around the vagus nerve. Stimulation with intensity of 1.5 mA to 1.75 mA, pulse width of 500 microseconds, and frequency of 30 Hz with stimulation set at 30 seconds on and 5 minutes off. Follow-up: **minimum 12 months** Conflict of interest: None.	**Response** Patients were considered as responders if they had a reduction in $HDRS_{21}$ score of more than 50% from baseline. Patients were considered 'remitted' if HDRS total score was ≤ 10 at study endpoint. None of the patients were responders within the first week of follow-up. 56% (5/9) of patients were responders at final follow-up and 44% (4/9) were in remission. Patient 2 A 65-year-old woman with severe resistant major unipolar depression for 10 years had a HDRE score of 35 points at baseline. At 2-year follow-up with VNS the HDRS score had fallen to 5 points (remission). At 6-year follow-up the patient complained of gradual recurrence of depressive symptoms and HDRS score was 30. It was found that the stimulator generator battery had depleted. Once replaced the HDRS score had fallen to 20 points at a further 3-month follow-up.	**Complications** No major adverse events including infection or arrhythmia occurred during the procedure or the postoperative period. Hoarseness was observed in 100% (9/9) of patients but decreased with time.	Prospective study. Patient accrual method not reported. Follow-up described individually for each patient; mean or median follow-up period is not described. Authors state that there is still much to know about the pathophysiological characteristics of depressive disorders and about its heterogeneity, in order to address which patients are more likely to benefit from VNS.

Validity and generalisability of the studies

- Inclusion criteria vary across and within studies in terms of severity of depression, and definition of treatment resistance.
- Many studies reported relatively short-term follow-up, and there may be the possibility of relapse as with other treatment options for depression.
- Studies included patients receiving concomitant treatment; it may be difficult to establish the proportion of benefit derived from VNS.
- There is limited evidence from randomised studies.
- It is theoretically possible that some of the observed improvements in depression described in studies reflect either 'natural history' related improvement or a potential placebo effect.
- There are scant details in the literature about the 'dose' of VNS (for example, frequency and amplitude used by patients).
- Aftercare protocols and potential for concomitant therapies (drug-based or psychological) are not described consistently in literature.

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Prof. H D Critchley (National Patient Safety Agency), Mr S Eljamel (Society of British Neurological Surgeons), Dr R H McAllister-Williams (Royal College of Psychiatrists), Dr K Matthews (Royal College of Psychiatrists), Mr D McLoughlin (Royal College of Psychiatrists).

- Two Specialist Advisers categorised the procedure as novel and of uncertain safety and efficacy, and two that it was established and no longer new.
- The main comparator to the procedure would be Best medical therapy, ablative neurosurgery, or ECT.

- Key efficacy outcomes to assess efficacy of this procedure include depression scale scores, quality-of-life indicators, and decrease in use of adjunct medication for depression or use of adjunctive services.

- Anecdotal adverse events following the procedure include glottis spasm, coughing, shortness of breath on exertion and hoarseness.
- Additional theoretical adverse events may include arrthymias, asystole, cognitive disturbance (memory problems, confusion, fatigue), vocal chord paralysis, diarrhoea or local inflammation.
- One specialist adviser commented that little is known about the efficacy in subgroups.
- The procedure requires neurosurgical facilities, and MDT involvement.
- Patients receiving this procedure in the UK are an exceedingly small proportion of those with depression.
- If found to be safe and efficacious most advisers thought it likely that the procedure will be offered at less than ten specialist centres, but one suggested that it would be made available at a minority of district general hospitals, but at least ten.

Patient Commentators' opinions

- NICE's Patient and Public Involvement Programme were unable to obtain patient commentary for this procedure.

Issues for consideration by IPAC

- Studies included in the systematic review by Daban (2008) have not been included in this overview to avoid double counting of patients.
- Some studies included patients in the depressive phase of bipolar disorder. Clinical outcomes of these patients may be difficult to interpret because of the possible change to manic phase.

- It is difficult to exclude the possibility of duplicate publication of the same patients within the studies included in table 2 of the overview. Some patients with longer follow-up may have been reported twice.
- Several authors admit that the precise mechanism of action of VNS in influencing depressive symptoms is not known.

References

1 Daban C, Martinez-Aran A, Cruz N et al. (2008) Safety and efficacy of vagus nerve stimulation in treatment-resistant depression. A systematic review. Journal of Affective Disorders 110: 1−15

2 Nahas Z, Teneback C, Chae JH et al. (2007) Serial vagus nerve stimulation functional MRI in treatment-resistant depression. Neuropsychopharmacology 32:1649−60

3 Nierenberg AA, Alpert JE, Gardner-Schuster EE et al. (2008) Vagus nerve stimulation: 2-year outcomes for bipolar versus unipolar treatment-resistant depression. Biological Psychiatry 64: 455−60

4 Sackeim HA, Brannan SK, Rush AJ et al. (2007) Durability of antidepressant response to vagus nerve stimulation (VNS). International Journal of Neuropsychopharmacology 10: 817−26

5 Schlaepfer TE, Frick C, Zobel A et al. (2008) Vagus nerve stimulation for depression: efficacy and safety in a European study. Psychological Medicine 38: 651−61 (erratum in Psychological Medicine 38: 1067)

6 Franzini A, Messina G, Marras C et al. (2008) Hamilton rating scale for depression-21 modifications in patients with vagal nerve stimulation for treatment of treatment-resistant depression: Series report. Neuromodulation 11: 267−71

7 Sperling W, Reulbach U, Kornhuber J (2009) Clinical benefits and cost effectiveness of vagus nerve stimulation in long-term treatment of patients with major depression. Pharmacopsychiatry 42: 85−8

Appendix A: Additional papers on vagus nerve stimulation for treatment-resistant depression

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Conway CR, Chibnall JT, Tait RC (2008) Vagus nerve stimulation for depression: a case of a broken lead, depression relapse, revision surgery, and restoration of patient response. Brain stimulation 1 (3): 227−8	Case report n = 1 Follow-up = 2 years	In the VNS system there was a lead break at 42 months follow-up. During the period before revision surgery could be organised, the patient reported no depression at first but then began to deteriorate. Within 2 weeks of revision the HDRS score was 5 and all significant depressive symptoms had resolved.	Larger studies are included in table 2.
Frick C, Kosel M, Schlaepfer TE et al. (2005) Incident mania during therapy with vagus nerve stimulation. Journal of ECT 21 (3): 197	Case report n = 1 Follow-up = 6 months	The patient was admitted to hospital with an episode of acute mania. The patient was stabilised with medication with VNS remaining turned on.	Safety outcome already reported in studies in table 2 of the overview.
Husain MM, Stegman D, Trevino K (2005) Pregnancy and delivery while receiving vagus nerve stimulation for the treatment of major depression: a case report. Annals of General Psychiatry 4: 16	Case report n = 1 Follow-up = 2 years	VNS therapy provided effective treatment for treatment-resistant depression during pregnancy and delivery. VNS was safe for the patient and her child.	Larger studies are included in table 2.
Schwartz TL, Costello A (2007) Charting a sustained response to vagus nerve stimulation in treatment-resistant major depressive disorder. Primary Psychiatry 14 (8): 66−8	Case report n = 1 Follow-up = 6 years	The patient maintained an improvement of > 50% over her baseline depressive state for the previous 6 years and reported corresponding improvements in her social functioning and quality of life. The therapy was well tolerated with no treatment-limiting adverse effects, and the stimulation device was proven durable.	Larger studies are included in table 2.
Warnell RL, Elahi N (2007) Introduction of vagus nerve stimulation into a maintenance electroconvulsive therapy regimen: a case study and cost analysis. Journal of ECT 23 (2): 114−9	Case report n = 1 Follow-up = 10 months	This patient improved with VNS and was able to discontinue electro convulsive therapy	Combined VNS and ECT treatment. Larger studies are included in table 2.

Appendix B: Related NICE guidance for vagus nerve stimulation for treatment-resistant depression

Guidance	Recommendations
Interventional procedures	**Vagus nerve stimulation for refractory epilepsy in children. NICE interventional procedures guidance 50 (2004)** 1.1 Current evidence on the safety and efficacy of vagus nerve stimulation for refractory epilepsy in children appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 The procedure should only be undertaken by specialist paediatric epilepsy teams. 1.3 Almost all the current evidence on the efficacy of the procedure relates to reducing seizure frequency only. However the effect on quality of life remains uncertain. Future audit and research should include quality of life measures. Patients, carers and children should be informed about the unpredictability of benefit. Use of the Institute's Information for the Public is recommended. **Transcranial magnetic stimulation for severe depression. NICE interventional procedures guidance 242 (2007)** 1.1 Current evidence suggests that there are no major safety concerns associated with transcranial magnetic stimulation (TMS) for severe depression. There is uncertainty about the procedure's clinical efficacy, which may depend on higher intensity, greater frequency, bilateral application and/or longer treatment durations than have appeared in the evidence to date. TMS should therefore be performed only in research studies designed to investigate these factors 1.2 Future research should aim to address patient selection criteria, the optimal use of this procedure in relation to other treatments, and the duration of any treatment effect. Clinicians should collaborate to ensure that studies are sufficiently large to be adequately powered. The Institute may review the procedure upon publication of further evidence.
Clinical guidelines	**Depression (amended): management of depression in primary and secondary care. NICE clinical guideline 23 (2007)**

	1.6.2.14 When a patient's depression has failed to respond to various strategies for augmentation and combination treatments, referral to a clinician with a specialist interest in treating depression should be considered.

Appendix C: Literature search for vagus nerve stimulation for treatment-resistant depression

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	06/05/2009	2009, Issue 2
Database of Abstracts of Reviews of Effects – DARE (CRD website)	06/05/2009	-
HTA database (CRD website)	06/05/2009	-
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	06/05/2009	2009, issue 2
MEDLINE (Ovid)	07/05/2009	1950 to May Week 1 2009
MEDLINE In-Process (Ovid)	07/05/2009	May 06, 2009
EMBASE (Ovid)	06/05/2009	1980 to 2009 Week 18
CINAHL (NLH Search 2.0/)	06/05/2009	1981-Present
BLIC (Dialog DataStar)	06/05/2009	-
PsycINFO	06/05/2009	1967 to May Week 1 2009

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Depression/
2	exp Depressive Disorder/
3	exp Mood Disorders/
4	exp Bipolar Disorder/
5	Depression, Postpartum/
6	((Depress* or Mood* or Bipolar* or Bi-polar* or Season* or SAD* or Dysthymic*) adj3 (Disorder* or Episode* or postpartum*)).tw.
7	Depression*.tw.
8	Season* Affect* Disorder*.tw.
9	or/1-8
10	Vagus Nerve Stimulation/
11	VNS.tw.
12	(Vagus* adj3 Nerve* Stimulat*).tw.

13	exp Vagus Nerve/
14	or/10-13
15	Electric Stimulation Therapy/
16	(Electric* adj3 (therap* or stimulat* or pulse*)).tw.
17	Electrotherap*.tw.
18	or/15-17
19	18 and 14
20	19 and 9
21	Animals/ not Humans/
22	20 not 21
23	from 22 keep 1-143