Advanced Interventions Service

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# Vagus Nerve Stimulation (VNS) for bipolar disorder: frequently-asked-questions (FAQ) for clinicians and commissioning groups

# 1. Introduction

This FAQ is designed to provide specific answers to most of the questions that clinicians might have when making an application for an Individual Funding Request (IFR) for Vagus Nerve Stimulation (VNS) for bipolar disorder. Consequently, it is also written with the expectation that it (or the information within it) might be sent alongside the application in order to pre-empt an initial funding rejection on the basis that the procedure was not understood well-enough and/or that specific information was not included.

This information is not intended to replace a patient-information leaflet (available on request) but instead provides information that is intended to be much more relevant to commissioning groups. The document also includes a reasonably-extensive bibliography to provide additional sources of information that might be helpful when processing the IFR.

# 2. An overview of Vagus Nerve Stimulation (VNS)

## 2.1 Is this a new or experimental procedure?

No. VNS was first introduced as a treatment for epilepsy as long ago as 1990 and trials of VNS for depression were first published in 2000. Since then, there have been large European studies of VNS for depression (Bajbouj, Merkl, Schlaepfer*, et al*, 2010) and there are five-and six-year outcome data reported for large cohorts of patients with depression (Desbeaumes Jodoin, Richer, Miron*, et al*, 2018; Trottier-Duclos, Desbeaumes Jodoin, Fournier-Gosselin*, et al*, 2018) as well as bipolar depression (McAllister-Williams, Sousa, Kumar*, et al*, 2020).

## 2.2 What does the surgery involve?

In order to deliver electrical pulses to the Vagus nerve, it is necessary to wrap a small stimulating electrode around the nerve. VNS is applied to the left Vagus nerve. This procedure is performed by a neurosurgeon, under a general anaesthetic. The stimulating electrode is then attached by a small cable to a medical electrical pulse generator (see Picture 1. below). Thereafter, this small battery powered electronic device can be implanted under the skin on the upper chest wall (see Picture 2. below). This procedure is performed at the same time as the electrode is attached to the Vagus nerve. The whole procedure takes approximately one and a half hours.


Picture 1

Picture 2

## 2.3 Is it evidence-based?

Some of the following information applies to unipolar depression, since VNS has been used in this patient population more commonly than bipolar depression. However, chronic bipolar depression appears to behave similarly to chronic unipolar depression and so the outcomes are unlikely to be very different. Also, many of the clinical trials and cohort studies have included both unipolar and bipolar depression.

### 2.3.1 Randomised-controlled trials

There is only one randomised, controlled trial of VNS for depression and whilst it found benefits for VNS compared to treatment-as-usual (TAU) at 12-weeks on its secondary outcome measures, it was almost certainly too short to observe consistent treatment effects (George, Rush, Marangell*, et al*, 2005).

### 2.3.2 Cohort studies

For interventions where it is difficult to perform long-term RCTs, the best evidence comes from prospective clinical audits where cohorts of patients are followed-up over time. Published data on five-year outcomes in such groups (compared to treatment-as-usual) suggest that at five years, those who received VNS + TAU were more likely to achieve cumulative response than those who received TAU alone: 67.6% vs 40.9%; NNT = 4. Similarly, remission rates were higher in those who received VNS: 43.3% vs 25.7%, NNT = 6 (Aaronson, Sears, Ruvuna*, et al*, 2017).

For patients with bipolar disorder, similar outcomes have been found. Over 5-year follow-up, around two-thirds of patients (63%) in the VNS + TAU group had an initial response compared with 39% of participants in the TAU group. This is equivalent to an NNT of 4.2. The NNT for maintenance of response is 4.7, suggesting that those who achieve response are more likely to maintain it with VNS (McAllister-Williams, Sousa, Kumar*, et al*, 2020).

### 2.3.3 Outcomes in more chronic patients

In order to answer the question of whether VNS might be helpful in people who were more chronic and had higher levels of treatment resistance than those in clinical trials, we examined outcomes in those with strictly-defined unipolar depression who have failed to respond to an average of 9 previous treatment trials and found that around one-third of people met criteria for response at 12-months (Christmas, Steele, Tolomeo*, et al*, 2013).

# 3. The Advanced Interventions Service (AIS)

## 3.1 What is the AIS?

The Dundee Advanced Interventions Service was commissioned by NHS Scotland in 2006 to provide comprehensive, multidisciplinary clinical assessments for patients with chronic, treatment-refractory depression (TRD) and Obsessive Compulsive Disorder (OCD); and in a small number of cases, to provide neurosurgical treatment.

The Dundee service represents one of only a few clinical teams internationally who provide neurosurgical interventions for psychiatric disorders. The provision of psychiatric neurosurgery by a multidisciplinary / multi-professional team with members drawn from psychiatry, neurosurgery, psychotherapy, and mental health nursing is, to our knowledge, entirely unique internationally. However, it is only by drawing on such multidisciplinary expertise within an integrated clinical team that patients with such disabling, long-term, healthcare needs can be provided with comprehensive, bespoke, treatment plans that best meet those needs

## 3.2 How many people are seen and receive surgery?

Each year, the service receives around 60 referrals and sees approximately 40 patients from all over the UK. Every patient receives a comprehensive set of treatment recommendations but only a small number of people are offered neurosurgical treatment.

The Advanced Interventions Service has performed 16 VNS procedures in the last 10-12 years, mainly for treatment-refractory depression. There are probably no other centres in the UK with as much experience in VNS for psychiatric disorders.

# 4. Background

## 4.1 If bipolar disorder is not rare, why is this an 'exceptional clinical circumstance'?

Current NHS England guidance on Individual Funding Requests (IFRs) states: "*An IFR application is appropriate if you: Consider patient to be clinically exceptional compared to other patients excluded from funding as set out in a particular policy…*" (NHS Commissioning Board, 2013). The policy goes on to say: "…*you must show that your patient is very different from others in a group of patients with the same condition/stage of the disease and has clinical features that mean that they will derive much more benefit from the treatment you are requesting*."

Only a very small number of people will undergo neuromodulatory treatment for depression or bipolar disorder worldwide each year. We would, therefore, argue that the exceptionality comes not from the disorder itself but from the demonstration that all other reasonable treatment options have been shown to be ineffective and/or other treatment options offer very little potential for benefit.

## 4.2 Can't the local team continue to try other treatments?

Of course, but there isn't evidence that they're going to be effective. Just because there is a clinical trial of a new drug that shows benefit it doesn't mean it will work in all patients. Most drug trials in bipolar depression would only be applicable to 1-in-3 patients in clinical practice, with around two-thirds likely to be excluded (Hoertel, Le Strat, Lavaud*, et al*, 2013).

As suggested above, new-to-market antidepressants, mood stabilisers, and antipsychotics are not going to be applicable to patients who are considering neuromodulation treatments such as VNS and will lack evidence to support their use in such populations. Ultimately, continually trying endless combinations of medications with little realistic chance of success is rarely in the patient's best interests.

## 4.3 How do these patients differ from other patients with bipolar disorder?

These patients differ in a number of important ways:

1. The average duration of a depressive episode in the general population is 3 months (Spijker, de Graaf, Bijl*, et al*, 2002). Patients undergoing VNS have had an episode of depression that is 24 times longer than this.
2. Patients in secondary care have typically had three 'adequate' trials. Neurosurgical patients have had 3-4 times as much as this, and in many cases more.
3. The average severity of depression for patients undergoing VNS (based on 17-item Hamilton Depression Rating Scale) is 25. This is equivalent to 'severe' depression (Zimmerman, Martinez, Young*, et al*, 2013). The average depression severity for antidepressant trials is 22 (Kellner, Kaicher, Banerjee*, et al*, 2015) and it is slightly lower in psychotherapy trials.[1] Severe depression requires a score of 24 or above (Zimmerman, Martinez, Young*, et al*, 2013) which means that neither antidepressants nor psychotherapy have consistent evidence of benefit for severe depression.

## 4.4 What's the likelihood of response if nothing is done?

The chances of sustained improvement with 'treatment-as-usual' are very low, although definitive studies haven't been conducted. TRD is highly-recurrent and at least 80% of people who achieve remission will relapse within one year. The estimated probability of recovery over a 10-year period is no higher than 40% (Fekadu, Wooderson, Markopoulo*, et al*, 2009).

For patients considering VNS, the likelihood of response will be much lower; particularly since all other reasonable treatment options have *already* been tried. Spontaneous improvement is generally unseen in this severity of depression and alongside the risk of perpetual depression and disability, there is an elevated risk of completed suicide. The lifetime risk of suicide in depression is in the region of 4-5%, but this risk increases for those that have previously had any inpatient treatment (and almost all VNS patients have). The suicide rate in this population may approach 20% (Simon & VonKorff, 1998).

## 4.5 Is this a last-resort?

No. We explain to patients considering it that it's one option along a treatment pathway and that most people will continue to need treatment and follow-up after treatment with VNS.

[1] Data available on request.

# 5. The treatment pathway for VNS

## 5.1 Where is the surgery performed?

We anticipate that implantation of VNS can be performed in Ninewells Hospital, Dundee.

## 5.2 What about assessment and follow-up?

Most initial assessments take place in Dundee and we would aim to conduct the follow-up assessments in Dundee as well. However, where people are unable to travel we would see them in the location closest to them. All packages of care are tailored to the individual.

## 5.3 If it's a rare procedure, how do the surgeons remain skilled?

The actual implantation procedure doesn't differ from VNS implantation for epilepsy. The key difference is the range and depth of the assessments conducted prior to agreeing VNS for a particular patient, and also the follow-up provided.

# 6. Governance arrangements

## 6.1 Why isn't VNS funded by NHS Scotland?

This was a decision made by the NHS Scotland. The Advanced Interventions Service believed that VNS was a valuable alternative to neurosurgery for a number of people, but funding decisions had to be made at a National level. VNS was defunded just before we published evidence to support the use of VNS in patients with treatment-refractory depression.

## 6.2 What about NHS Scotland?

All specialist services in Scotland are reviewed annually by NHS Scotland. Since its inception, the AIS has been reviewed by NHS Scotland and has published an annual report (available on our website[2]).

In 2011 the service underwent a planned major review [3]. Key findings included:

- "…*the current review finding that the Advanced Interventions Service has provided a highly valuable service for people from across Scotland and the rest of the UK. The review recommends that the Advanced Interventions Service should continue to be nationally designated. The review recognises the high quality of the service provided*

[2] http://www.advancedinterventions.org.uk/index.php/the-service/reports-to-nsd.html

[3] http://www.advancedinterventions.org.uk/index.php/most-recent-reports/31-ais-reports-nsd-2011/8-5-year-review-of-the-advanced-interventions-service.html

*and the clinically significant improvements in mental health experienced by people with highly chronic and severe depression following a neurosurgical intervention carried out by the service*."

### 6.3 Is the Advanced Interventions Service an NHS Tayside service?

No, it's an NHS Scotland service that is hosted by NHS Tayside. The service adheres to the clinical governance arrangements of the host Board but its funding, continued commissioning, and higher-level operational oversight are the responsibility of National Services Division of NHS Scotland.

## 7. Clinical and functional outcomes

### 7.1 How often do you review patients?

All patients undergoing anterior VNS undergo neuropsychological testing before surgery, immediately after surgery, and at 1-year, 2-year, and five-year follow-up.

Although it's not part of our formally-commissioned activity, we will remain in contact with patients and their local teams for as long as possible. For example, we are happy to provide advice to local teams long after the patient has had VNS and we would aim to be involved in major treatment decisions for as long as the patient and their local team would wish us to be.

### 7.2 How is outcome measured?

The primary indication for VNS in these patients is persistent (or highly-recurrent) depression. Therefore, depression severity is rated by the clinician using the Hamilton and MADRS depression rating scales (Hamilton, 1960; Montgomery & Åsberg, 1979). We also use self-report scales (Rush, Gullion, Basco*, et al*, 1996) to measure depressive symptoms. More details can be found on our website and are available on request.

Alongside symptom ratings, we collect lots of information on health-related quality-of-life and we also collect outcomes relating to social and interpersonal functioning.

If patients have not been using prospective ratings of mood on a daily/ weekly basis, we will typically require them to do this since bipolar disorder is, by nature, a cyclical mood disorder and we need enough information on cycle frequency and severity to be able to form reasonable conclusions about the effects of VNS on both the underlying depressive symptoms but also the stability of the illness itself.

## 7.3 What is a 'response' and what is 'remission'?

We use the conventional definitions used worldwide: a 'response' is ≥ 50% improvement in baseline symptom severity; 'remission' is a score ≤ 7 on the Hamilton Rating Scale for Depression or ≤ 10 on the MADRS rating scale. Remission is essentially an absence of clinically-significant depressive symptoms.

## 7.4 What percentage of people will respond?

We have reported in detail on the clinical outcomes for patients treated with VNS in Dundee (Christmas, Steele, Tolomeo*, et al*, 2013). At 12-months we found that 31% of people met criteria for 'response'. Assuming that the response rate for 'treatment-as-usual' in this population would be no higher than 5%, this means that the 'number-needed-to-treat' (NNT) for VNS is 4. This is better than the NNT for antidepressants (7-8) and well-within the magnitude of treatment effect that is normally approved by NICE.

In bipolar patients specifically, the best information comes from large 'registry-based' studies that follow-up people who have had the procedure. Over a 5-year follow-up, around two-thirds of patients (63%) in the VNS group had an initial response compared with 39% of participants in the treatment-as-usual group (McAllister-Williams, Sousa, Kumar*, et al*, 2020).

## 7.5 What about side-effects?

Since its inception, the service has used extensive testing in order to detect possible adverse effects from ablative neurosurgery. For example, we use the CANTAB battery for neuropsychological testing and we use validated rating scales (*e.g.* SAFTEE-SI) for treatment-emergent adverse effects.

The most commonly-reported adverse effects in the Dundee cohort (N=13) have been: hoarseness (46.2%); coughing (15.4%); throat discomfort (23.1%); and mild swallowing difficulties (7.7%). All of these are consistent with the world literature and are related to active stimulation. In almost all cases, adverse effects emerging in early treatment will improve over time. We have observed no serious events occurred which required hospitalisation or explantation of the device.

In brief, most people tolerate VNS without significant problems and even if side effects do occur, they are usually manageable by changing the stimulation settings and do not interfere with treatment adherence.

## 7.6 Is it cost-effective?

Overall service costs for treatment-refractory depressive symptoms are high; particularly when you consider the costs of inpatient admission (Crown, Finkelstein, Berndt*, et al*, 2002). VNS patients in Dundee have had an average of 3.4 ± 1.9 inpatient admissions during their lifetime, with an average total duration of inpatient stay of 20.2 ± 27.5 weeks. Assuming that each occupied bed day costs an average of £466 (Scottish figures)[4], the total cost for inpatient admissions before VNS for the average patient is £65,892. Reducing this by 30% in the years following implantation would make the procedure cost-neutral, irrespective of the improvements in the patient's symptoms and quality of life.

Another potential cost saving is in a reduced need for ECT. The typical VNS patient is someone for whom maintenance ECT may be the only thing keeping someone out of hospital. However, long-term maintenance ECT is associated with an increasing risk of cognitive adverse effects and many people find maintenance ECT unacceptable; particularly if it isn't resulting in significant symptom improvement. A typical ECT treatment costs in the region of £1,000. This means that someone who is requiring 24 ECT treatments per year (fortnightly ECT), will result in treatment costs of £24,000 per year. For those that require hospital admission, the treatment costs will be higher. Assuming a five-year timescale, reducing the need for ECT by one-fifth each year would result in the treatment being cost-neutral.

About 10% of all NHS costs are made up of physical and comorbid complications of untreated mental health disorders. This means that treating a primary depressive illness can reduce downstream and associated costs across a range of care pathways. The costs of treatment for those who don't respond (compared to those who do respond) are approximately three times higher (McIntyre & O'Donovan, 2004).

Although most of the data comes from studies in unipolar depression, there is evidence that VNS may reduce overall treatment costs, leading some to conclude that: "*The reduction in physician consultations and prescription drugs further underlines the conclusion that VNS is a clinically effective and cost-effective treatment option for therapy-resistant depression*" (Sperling, Reulbach & Kornhuber, 2009) and, "*Lowered costs post-implantation with evidence of response to VNS suggest the therapy represents an option for carefully screened [people with treatment-refractory depression] who have failed other therapies*." (Feldman, Dunner, Muller*, et al*, 2013)

[4] NHS Scotland Costs Book, 2015.

### 7.7 What do current guidelines say?

The BAP Guidelines suggest that: "*VNS…could be considered in patients with chronic and/or recurrent depression who have failed to respond to four or more antidepressant treatments. [VNS] should only be undertaken in specialist centres with prospective outcome evaluation and where provision for long-term follow-up is available*" (Cleare, Pariante, Young, et al, 2015).

## 8. Other treatment options for chronic depression

### 8.1 You've listed quite a few below. Should they be all be tried before surgery?

The following is a brief overview of some of the alternatives to neurosurgery that people often ask us about. All treatment options should be tailored to the individual patient and a listing here doesn't mean that it provides a viable alternative to VNS. This list generally includes information on interventions that PCTs or commissioning groups have specifically asked about in the past.

### 8.2 Repetitive Transcranial Magnetic Stimulation and variants (rTMS, T-PEMF)

BAP Guidelines state that: "*rTMS… has limited evidence of efficacy but could be considered for individuals who are intolerant of other treatments and who have failed to respond to initial treatment strategies. However, the availability of rTMS is limited, and evidence to support benefit in patients who are unresponsive to more than 3–4 antidepressant treatments is currently lacking*." (Cleare, Pariante, Young*, et al*, 2015)

In most studies, the duration of follow-up is short (typically 4 weeks) and patients have less chronic and less severe forms of illness. There isn't evidence to suggest that rTMS (or variants thereof) represent treatment alternatives for this patient group at the current time. Conversely, VNS has prospective outcome data over five years and those that show response will typically maintain this over long periods of time.

### 8.3 Transcranial Direct Current Stimulation (tDCS)

tDCS is not currently considered a viable treatment option for people with moderate-severe depression (Cleare, Pariante, Young*, et al*, 2015). There are no studies of tDCS for depression in people with severe, chronic, treatment-refractory depression and almost all outcome studies are in relatively treatment-naïve patients. Follow-up duration in most studies is rarely more than four weeks.

## 8.4 What about other psychological therapies?

Although several psychological therapies have been shown to be beneficial for many people with non-chronic mild-moderate depression, there are no clinical trials of psychological therapy in patients who have severe and chronic depression.

Although our post-operative treatment recommendations will usually include some form of psychological/behavioural therapy, there is an expectation that it will be easy-to-implement by local services and will focus more on improving function in the recovery period than addressing underlying psychological issues. Further, we would expect that such treatments (*e.g.* behavioural activation) would be dependent on early signs of improvement after implantation.

Given what we know about the failure of psychological therapies in chronic depression, it can often be counter-productive to engage a severely-unwell individual in multiple trials of different therapies when they have already failed to benefit from the best-evidenced therapies available. There isn't, for example, compelling evidence that one treatment modality is better than any others (Barth, Munder, Gerger*, et al*, 2013; Cuijpers, Berking, Andersson*, et al*, 2013).

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