Clinical Commissioning Policy: Deep Brain Stimulation for Refractory Epilepsy (all ages)

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Clinical Commissioning Policy: Deep Brain Stimulation for Refractory Epilepsy (all ages)

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Policy Statement

NHS England will not routinely commission deep brain stimulation for refractory epilepsy in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain Language Summary

About current treatments

Epilepsy is a neurological disorder where the patient suffers from fits (seizures). These seizures are the result of excessive and abnormal activity in the brain. These can be brief and nearly undetectable or go on for long periods of vigorous shaking. People with epilepsy are at an increased risk of sudden unexpected death.

In many patients some of these seizures are controlled with medication. Patients whose seizures do not respond to drug therapy are considered to have refractory epilepsy. Other surgical treatments can be considered for these patients but these are still not always effective for everyone suffering from refractory epilepsy.

About the new treatment

This is a procedure in which stimulating electrodes are placed into the deep structures of the brain. The electrodes are connected to an implanted pulse generator which is battery powered. It is suggested that successful deep brain stimulation (DBS) allows better control and minimisation of a patient's epileptic seizures and that there are gains in control of the seizure severity and frequency.

What we have decided

NHS England has carefully reviewed the evidence to treat refractory epilepsy with deep brain stimulation. We have concluded that there is not enough evidence to make the treatment available at this time.

1 Introduction

Deep brain stimulation (DBS) is a surgical treatment involving the implantation of a medical device which delivers electrical impulses to specific parts of the brain. DBS in selected brain regions is an accepted treatment for movement disorders (Parkinson's, dystonia, tremor) and has also been used for chronic pain, treatment resistant depression. DBS directly changes brain activity in a controlled manner, the effects are reversible (unlike those of lesioning techniques).

DBS leads are placed to different targets, with different techniques in the brain according to the disorder being treated. DBS for refractory epilepsy targets the Anterior Nucleus of the Thalmus (ANT). The ANT represents an attractive stimulation target due to its widespread thalamocortical projections.

The DBS system consists of three components: the implanted pulse generator (IPG), the electrode (lead), and an optional extension. All three components are surgically implanted inside the body. For epilepsy a hole is drilled in the skull and the electrode is inserted accurately by stereotactic methodology to an anatomical target, verified by imaging post-procedure. The installation of the IPG and lead occurs under general anaesthesia. The IPG is then programmed to optimize symptom suppression and control side effects. The patient is usually managed by a multidisciplinary team.

Seizures are controllable with medication in about 70% of cases. Patients whose seizures do not respond to anti-epileptic drug therapy are considered to have refractory epilepsy.

In a smaller group of cases the seizures are both refractory to drug treatment and severely disabling, and it is this group that may be considered for other treatments including vagal nerve stimulation and epilepsy surgery. Some patients continue to have severe disabling epilepsy and thus there is an unmet need.

2 Definitions

Anterior Nucleus of the Thalmus (ANT): a collection of nuclei at the rostral end of the dorsal thalamus.

Anti-epileptic drugs: a diverse group of pharmacological agents (drugs) used in the treatment of epileptic seizures.
Deep brain stimulation (DBS): a surgical treatment involving the implantation of a medical device called a brain pacemaker, which sends electrical impulses to specific parts of the brain.
Implanted pulse generator (IPG): a component that is surgically implanted inside the body and programmed to optimize symptom suppression.
Refractory epilepsy: Patients whose seizures do not respond to drug therapy are considered to have refractory epilepsy.
Vagal nerve stimulation: implantation of a device that prevents seizures by sending regular, mild pulses of electrical energy to the brain via the vagus nerve.

3 Aims and Objectives

This policy aims to consider the evidence available for DBS for refractory epilepsy and establish:

1. Is there sufficiently robust evidence of clinical effectiveness and safety to support the use of DBS for patients with refractory epilepsy?

2. If the evidence is sufficiently robust, what criteria should be used to identify suitable patients to be considered for DBS treatment for refractory epilepsy?

4 Epidemiology and Needs Assessment

Epilepsy is a highly prevalent disorder that is a major cause of morbidity in patients throughout the world. Nearly 1% of the population suffers from epilepsy, with an annual incidence of 50/100,000 people (Sander 2003). In 60%–70% of people with epilepsy, treatment with antiepileptic medications results in seizure remission (Sander 2003). The remaining patients, in whom symptoms are refractory to medications, currently have relatively limited alternative treatment options.

In England, approximately 600,000 people in the UK (in 2011) had a diagnosis of epilepsy and were taking anti-epileptic drugs (Joint Epilepsy Council of the UK and

Ireland 2011). Based on 2010 census estimates, prevalence of epilepsy in England was 0.95%, 1.06% in Wales, 1.03% in Scotland and 1.11% in Northern Ireland.

The seizures in approximately two-thirds of people with epilepsy can be successfully controlled with current available anti-epileptic drugs, leaving one third with uncontrolled epilepsy (Laxer et al 2014). The proportion of these who would be eligible for and accept invasive procedures such as resective surgery or neurostimulation will be lower, however, the exact proportion is not clear.

The most effective option in patients with medically refractory epilepsy is resective epilepsy surgery, which involves the excision of the part of the brain causing the epilepsy. This requires that the seizures that arise from a single focus and do not arise from an eloquent area. In patients with well-defined epileptic zones, this can offer a high likelihood of excellent long-term seizure control, or at least significant improvement. In medically intractable patients in whom resection fails to control seizures, or for patients who are not appropriate candidates for surgery, there are a limited number of other available options.

Typically, refractory epileptic patients have frequent admission to hospitals and may require significant support from other services. Epileptic patients tend to have a lower life expectancy and are at risk of sudden death in epilepsy (SUDEP). Consequently, any treatment that reduces seizures may reduce mortality and reduce morbidity.

5 Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of deep brain stimulation for refractory epilepsy

An evidence review was undertaken to identify studies. One Cochrane systematic review of DBS for epilepsy met the inclusion criteria of the evidence review and is included (Sprengers et al 2014). No studies were found that directly compared DBS with other neurostimulation methods like Vagal Nerve Stimulation (VNS) or NeuroPace. Although a systematic review of VNS and a Randomised Control Trial (RCT) of NeuroPace for refractory epilepsy was identified, these results cannot be

compared directly with the outcomes reported for patients being treated with DBS and no firm conclusions on the comparative effectiveness of these techniques can be drawn.

The most reliable data is from the large RCT (SANTE trial) of DBS targeted at the anterior nucleus of the thalamus bilaterally, and included 109 refractory epilepsy patients (average age 36 years). These patients had epilepsy for an average of 22.3 years, had a median of 19.5 seizures per month at baseline, had failed to respond to at least 3 AEDs, and were mostly currently taking 2 or more AEDs. Just over half (53.6%) had previous VNS (29.1%) or resective surgery (9.1%), or both (15.5%). The SANTE trial found a mean 29% decrease in seizure frequency with DBS (stimulation 'on') when compared to control (stimulation 'off') over the 3 month double blind period (p=0.0017). Actual seizure frequencies at the end of the trial were not reported. One outlier participant who experienced a large number of seizures each time the DBS stimulation was switched on was excluded from these analyses of mean difference in seizures.

The mean and median reductions reported at the end of 3 months were calculated to roughly equate to about 4 to 6 fewer seizures per month with DBS than control in an individual with the median baseline seizure frequency of 19.5 seizures per month (reviewer calculated).

The trial also found that proportion of participants with injuries resulting from seizures were significantly reduced by DBS over 3 months (7% with DBS vs. 26% with control; p=0.01) (NICE 2012). There was no significant difference between groups in the proportion of participants who were seizure free after 3 months, or the proportion who had 50% or greater reduction in seizure frequency (response rate: 29.6% with DBS vs. 25.9% with control, OR 1.20, 95% CI 0.52 to 2.80) (Spengers et al 2014).

Long term follow up of the SANTE RCT's participants once they were all receiving DBS found that median reduction in seizure frequency at 1 year was 41% and at 5 years was 69% compared to baseline (p<0.001 for both time points). This would equate to a change in median seizure frequency per month from 19.5 at baseline to about 6 at the end of 5 years (reviewer calculated). Only 76% of participants

(83/109) were able to be followed up at 5 years. Using last observation carried forward analysis provided similar results to completer analysis. In a “worst case” scenario, if all failed to follow up patients were considered to have 100% worsening of seizures from baseline, there was still a 50% median seizure frequency reduction at 5 years, although this difference was not statistically significant.

DBS did not improve quality of life or seizure severity at 3 months. However, five year follow up did show a statistically significant improvement in quality of life and seizure severity from baseline with DBS. At 1 year, 46% of the 102 participants followed up had experienced a clinically significant improvement in quality of life; the corresponding figure at 5 years was 48% of the 80 participants followed up. Without a control group to act as a comparator results of long term follow up should be interpreted cautiously. Given the severity of the condition, long term sham controlled studies are unlikely to be conducted.

The other RCTs of DBS included in the Cochrane review targeted different deep brain regions and were much smaller (2 to 13 participants), therefore firm conclusions cannot be based on their findings (Spengers et al 2014).

One RCT of NeuroPace (n=191) included participants with refractory partial onset seizures, with about a mean of 36 to 37 seizures per month at baseline, epilepsy duration between 2 and 57 years, and about a third had prior surgery and a third prior VNS. In order to receive NeuroPace, 1 to 2 seizure foci had to be identified which could be monitored and targeted by the device – this was not a specified requirement in the SANTE trial.

The NeuroPace trial found that NeuroPace reduced seizure frequency by 24.9% compared with control (95% CI -40.1% to -6.0%; actual seizure frequencies not reported), but did not significantly affect response rate or seizure freedom rate (Spengers et al 2014).

High-level VNS stimulation significantly increased response rate compared with low-level stimulation in a meta-analysis (4 RCTs, n=373; illustrative risk: 24.9% with high-level VNS vs. 14.4% with low-level VNS; RR 1.73, 95% CI 1.13 to 2.64;

p=0.01). Absolute reduction in seizure frequency or the proportion of individuals who were seizure free with high versus low frequency VNS was not reported in the review. The low-level stimulation used as a comparator in this trial may be having some effect, and not give a true representation of the effects of VNS versus no VNS (continued medical management alone).

In terms of safety, the SANTE RCT found that patient reported depression and memory impairment were significantly increased in the DBS group compared with control at 3 months (depression: 14.8% vs 1.8%, p=0.016; memory impairment: 13.0% vs 1.8%, p=0.032). Memory impairment was reported as not serious. However, neuropsychological tests did not show between group differences in mood or cognition at 3 months. Over long term follow up, 37.3% of participants had experienced depression events. These were considered device related in 3 out of 41 participants affected. Over a quarter of participants (27.3%) reported memory impairment during long term follow up, but none of the events was considered serious. Most of those affected by depression or memory impairment had a previous history of these conditions (66% and 50% respectively).

Data suggest that some patients experience benefit with DBS, but it is not possible to identify these patients in advance.

Asymptomatic intracranial haemorrhages were detected incidentally by neuroimaging in 4.5% of participants in the trial; none of these were clinically significant. Skin infection at the site of implantation was reported in 13% of the patients in the SANTE RCT.

The NeuroPace RCT included in the Cochrane review reported that 4.7% of participants (9/191) experienced intracranial haemorrhage, with most considered serious but none resulting in permanent neurological damage (Spengers et al 2014). Implant or incision site soft tissue infections occurred in 5.2% of patients receiving NeuroPace.

Compared to low level VNS, high level VNS significantly increased voice alteration and hoarseness (3 RCTs, n=334; RR 2.17, 99% CI 1.49 to 3.17), as well as

dyspnoea (2 RCTs, n=312; RR 2.45, 99% CI 1.07 to 5.60) (Panebianco et al 2015). There was no difference between these groups in cough, pain, paraesthesia, nausea, or headache. The side effects reported to be associated with high level VNS are less serious in nature than those attributed to DBS. This is likely to be at least in part due to the fact that in VNS electrodes are not implanted directly in the brain.

6 Documents which have informed this Policy

None.

7 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

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