Deep Brain Stimulation in Patients with Chronic Treatment Refractory Anorexia Nervosa: a Pilot Study

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The aims of this research project are:1) to establish the efficacy and feasibility of DBS as a last resort treatment in patients with chronic, treatment refractory AN. 2) to associate the efficacy and functional effects of DBS in patients with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Appetite and general nutritional disorders
Study type	Interventional

Summary

ID

NL-OMON47057

Source
ToetsingOnline

Brief title
DBS in Anorexia Nervosa

Condition

- Appetite and general nutritional disorders
- Eating disorders and disturbances
- Nervous system, skull and spine therapeutic procedures

Synonym
Anorexia nervosa; self starvation; eating disorder

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Anorexia nervosa, Deep Brain Stimulation, Neurobiology, Reward System

Outcome measures

Primary outcome

Treatment effects will be established using within-subject analyses comparing baseline characteristics (T-1 and T0) with patient reports during the optimization phase (T1 and T2) and after 6 months of the maintenance treatment period (T3) and at the end of the maintenance period (T4).

Primary outcome measurements are:

1. Physical outcome: Weight improvement/BMI

Clinical relevant improvement is defined as relative improvement of BMI of at least 30% compared to the pre-operative BMI or by normalisation of BMI, i.e. reaching a BMI of >= 18 (defined by consensus by D.D., A.E., J.S., M.O.)

2. Psychological outcome: Score on the Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS; Mazure e.a. 1994, Dutch translation by our department with back-translation to ensure conceptual equivalence)

Clinical relevant improvement is defined as a reduction in pre-operative YBC-EDS scores of al least 35% ánd a CGI-I score of 1 or 2.

3. Quality of life: Score on the EDQOL (Eating Disorders Quality of Life;

Engel

e.a. 2006)

Secondary outcome

Secondary outcome measurements (assessed at T-1 (pre surgery), T1 (1 month after surgery), T2 (optimization phase), T3 (6 months maintenance phase) and T4 (end of maintenance phase) include:

1. Additional psychological outcome:

a. Eating behaviour measured by assessing the quantity, quality and choice of food

b. Assessment of eating behaviour with the Eating Disorder Inventory (EDI-II; van Strien 2002), the Eating Disorder Examination Questionnaire (EDE-Q; Dutch translation by Jansen 2000), and the Nederlandse Vragenlijst voor Eetgedrag (NVE; van Strien e.a. 1986)

c. Assessment of body image disturbance (implicit level) with the Tactile Estimation Task (TET; Keizer e.a. in prep, Keizer e.a. 2012, Keizer e.a. 2011)

2. Quality of life:

Secondary outcomes include social function and quality of life using the EQ-5?6D (Euroqol 6 Dimension), the WHO-QOL BREF (World Health Organisation - Quality of Life), the MOS SF12?36 (Medical Outcome Study Short Form), the SDS (Sheehan Disability Scale), and the Q-LES-Q (Quality of Life Enjoyment and Satisfaction Questionnaire).

Additionaly, in order to study the functional efficacy of capsula interna Deep

Brain Stimulation in patients with anorexia nervosa, the following studies will

be performed:

1) effects of DBS on cerebral perfusion in response to specific tasks using

functional MRI

2) electrophysiologic assessment measured through electro-encepahlography (EEG)

3) changes in neuropsychological functioning

Study description

Background summary

The Department of Psychiatry of the AMC has the intention to start a pilot study with the objection to assess the efficacy and safety of Deep Brain Stimulation (DBS) in treatment-refractory anorexia nervosa (AN) patients.

Anorexia nervosa is a serious psychiatric disorder constituting a major public health problem. In about 20% of the cases the disease takes on a chronic course (Steinhausen 2002). With a crude mortality rate of 5,6% per decade (Sullivan 1995), AN has the highest mortality of all psychiatric disorders (Attia 2010). Up to date, there is no evidence-based treatment for AN (Agras e.a. 2008; Morris e.a. 2007; Guarda 2007).

Many parallels with regard to symptomatology between anorexia nervosa and obsessive compulsive disorder have been drawn. There is a high rate of comorbidity between eating disorders and anxiety disorders (Kaye e.a. 2006; Godart e.a. 2003; Speranza e.a. 2001). Numerous observers have documented the importance of the mesolimbic reward system in the pathophysiology of anorexia nervosa. The reward system is considered to be involved in several psychiatric disorders, a.o. obsessive compulsive disorder and addiction.

It is hypothesized that in anorexia nervosa there is a dysregulation of the reward system, in which 1) hyperactivity of cognitive networks in the dorsal neurocircuit directs motivated actions when the ability of the ventral striatal pathways to direct more automatic or intuitive motivated responses is impaired, or 2) the limbic-striatal information processing in the ventral circuit is too strongly inhibited by the dorsolateral prefrontal cortex and the parietal cortex.

Because of the many similarities between obsessive compulsive disorder and anorexia nervosa, both with regard to symptomatology and with regard to the brain systems and adaptive responses involved, it is conceivable that significant relapse and failure rates of current anorexia nervosa treatments may be at least in part the result of a dysregulated reward system.

Deep Brain Stimulation (DBS) is an innovative and promising approach for the treatment of patients with therapy-refractory reward-related psychiatric disorders by modulating the reward-circuitry in the brain (Bewernick e.a. 2010; Denys e.a. 2009; Schlaepfer e.a. 2008; Okun e.a. 2007; Greenberg e.a. 2006; Sturm e.a. 2003). The department of psychiatry of the Academical Medical Centre (AMC) Amsterdam is one of the few centers in Europe performing DBS for complex psychiatric disorders. Currently, our center has experience in obsessive-compulsive disorder, addiction and major depressive disorder. In all these disorders, DBS targets reward related brain areas such as the nucleus accumbens and the ventral striatum.

Modulating the reward circuitry in the brain in an attempt to *re-regulate* this dysregulation of the reward system, by means of deep brain stimulation of the ventral anterior limb of the internal capsula (theorizing that this has a positive influence on the reward deficits in anorexia nervosa, as well as positive effect on the overactivity of the corticolimbic mechanisms of the brain reward system), may provide significant and sustained improvement in anorexia nervosa symptoms and associated comorbidities and complications.

We propose to introduce DBS for chronic, therapy refractory anorexia nervosa (a) based on our clinical experience with DBS as a safe and effective treatment for therapy-refractory reward-related psychiatric disorders, (b) based on the literature on the (reward) neurocircuits involved in anorexia nervosa and (c) based on the existing knowledge of animal models and human imaging studies on anorexia nervosa.

Based on indications from clinical and animal studies, we have chosen the area above the nucleus accumbens (the ventral limb of the capsula interna) as target for stimulation.

Study objective

The aims of this research project are:
1) to establish the efficacy and feasibility of DBS as a last resort treatment in patients with chronic, treatment refractory AN.

2) to associate the efficacy and functional effects of DBS in patients with chronic, treatment refractory AN with changes in cerebral perfusion in response to specific tasks using functional MRI and with electrophysiologic assessement through electro-encephalography (EEG).

3) to assess safety of DBS in patients with chronic, treatment refractory AN assessing changes in neuropsychological functioning.

Study design

In this pilot study of Deep Brain Stimulation in patients with chronic treatment refractory anorexia nervosa, 6 adult patients (age 25-65) with chronic treatment refractory AN will be included, after written informed consent has been obtained, to participate in a 18 month prospective trial using high frequency DBS of the ventral anterior limb of the internal capsula.

The complete study comprises four sequential phases: (1) preparatory phase; (2) surgery phase; (3) optimization phase;; and (4) maintenance treatment phase.

Phase 1: Preoperative phase
The preparatory phase (T-1) is the period before the actual surgery, needed for the recruitment, selection and assessment of the patients. Neuroimaging, psychometric/psychiatric assessments, neuropsychological tests and affective information processing tasks will be conducted during this period.
Standard somatic and psychiatric care will be available to all patients throughout this period and if necessary patients may be hospitalized at the PsychMedUnit (PMU) of the psychiatric department of the AMC.

Phase 2: Surgery phase
During this phase (T0) the implantation of the electrodes and the stimulator will be performed according to standard procedures. The patient is admitted the day before surgery, and will be discharged from the department of neurosurgery one or several days after the procedure, depending on the psysical condition of the patient.
The implantation procedure is carried out entirely under general anaesthesia. After anaesthesia is started, a stereotactic frame will be applied to the head in order to facilitate the stereotactic electrode implantation. After frame application, a high resolution structural MRI is made to guide the surgeon in the planning of the operation. Then two electrodes (Medtronic Quad 3389) are implanted bilaterally with the tip of the electrodes in the core of the NAc.
The selected target point for the electrodes will be chosen in accordance with the atlas of Mai et al. (Mai et al., 2004; J.K. Mai, J. Assheuer and G. Paxinos, Atlas of the Human Brain (2nd ed.), Elsevier Academic, San Diego; Videen e.a. 2008) and transformed to the corresponding position in the patient*s brain.
After electrode implantation, the stereotactic frame is removed, and both electrodes are then connected via a subcutaneous extension cable to a neurostimulator, which is implanted in the infraclavicular region (see figure 3). The correct position of the electrodes will be comfirmed directly postoperatively with a CT-scan, and after several months with an MRI-scan.

If necessary, prolonged clinical observation is possible after surgery in the AMC (Psychiatric Medical Unit, or Department of Neurosurgery).

Phase 3: Optimization phase
The optimization phase lasts between 3 and 9 months. Immediately after recovery from surgery, the neurostimulator will stay in off mode during three weeks in order to prevent interference with the effects from surgery that may complicate the fine-tuning of the stimulation parameters (location, frequency, voltage). After these three weeks, the neurostimulator is switched *on* (T1) and fine-tuning/optimization of the neurostimulation will be performed during 3-6 months. If, thereafter, clinical improvement is still expected with additional changes in neurostimulator settings, a continuation of the fine-tuning phase is possible for 3 more months (until a maximum total duration of the optimization phase of 9 months), with assessments of improvement every 2 weeks until a plateau of effectiveness is reached. During the optimization phase the psychiatric and somatic condition and the potential development of a refeeding syndrome will be monitored closely by regular physical examination and laboratory tests. If necessary, patients can be admitted to the Psychiatric Medical Unit of the AMC.
Patients enter the next phase of the study after the optimization period is completed, which is (1) after at least three months of trial stimulation during which the stimulation parameter settings are determined that give the best clinical improvement, or (2) when after an extension of the optimization phase no (further) clinical improvement can be achieved. Clinical improvement will be quantified with 1) sustained weight improvement/BMI change, 2) score change from baseline on the Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS), 3) the Clinical Global Impressions Scale (CGI, Busner e.a. 2007; clinical improvement is defined as a CGI-Improvement (CGI-I) score of 1 or 2).

Phase 4: Maintenance period
The maintenance phase (T2) consists of a period of 12 months following the optimization period, with the stimulator *on*, to assess the long term effect of DBS on weight/BMI, comorbidity, and eating behaviour. During this period, when required, further optimization of stimulation parameters is allowed. After 6 months (T3) an interim-analysis will be performed.

Intervention

The intervention of this study will be Deep Brain Stimulation (DBS) in the ventral limb of the capsula interna. Deep Brain stimulation is an adjustable, reversible, non-destructive intervention using a surgically implanted medical device to deliver carefully controlled electrical pulses to precisely targeted areas of the brain. The stimulation can be programmed and adjusted non-invasively by a trained physician to maximize symptom control and minimize side effects. The ventral limb of the capsula interna has been chosen because both animal and human studies indicate that this location is promising for DBS treatment of anorexia nervosa and because this location has shown to be safe in

DBS studies among humans with other psychiatric/reward-related disorders such as OCD, depression, and addiction. In addition, the AMC has ample experience with DBS in this brain region, since more than 40 patients with OCD and with major depressive disorder have been treated following the same protocol.

Study burden and risks

Obviously the greatest burden on the patient during this study is the intervention itself. During the various phases of the study, the time burden on the patient varies and consists of ca. 30 hours in the preoperative phase, ca. 20 hours in the 1 week surgery phase and . Patients will be admitted to the hospital for 1-2 days during the surgery phase. .

In general, potential risks involved in DBS include the risks associated with the surgical procedure, including the risk of intracranial haemorrhage or infection and the associated neurological consequences. Studies on DBS in movement disorders have reported a 0% to 5% risk of intracerebral hemorraghe (de Koning e.a. 2011). Recent AMC-data show a rate of intracerebral hemorraghe of 1% and a rate of intracerebral infection of 2%. In addition, some patients may show some temporary neurological symptoms (e.g. eye movement abnormalities, transient diminished concentration and verbal perseverations) that generally disappear spontaneously or after some fine-tuning of the stimulator.
Acute mood changes during the first few days of stimulation of the ALIC and NAc have been reported, specifically transient sadness, anxiety and euphoria (sometimes to the extent of hypomanic and manic symptoms). In most cases, the acute mood changes appear to be transient. All hypomanic and manic episodes dissolved after the field density was readjusted by changing the voltage and/or the active contact (de Koning e.a. 2011).
The psychiatric condition and the potential development of hypomanic and/or manic symptoms will be closely monitored by a psychiatrist, especially during the first period of stimulation and after changing the stimulation settings. Patients will receive instructions to report hypomanic and/or manic symptoms immediately. In the case of hypomanic and/or manic symptoms, stimulation settings will be adjusted. If necessary, patients can be admitted to the Psychiatric Medical Unit of the AMC.

Patients with AN are predisposed to significant risk of multi-organ dysfunction related to starvation and purging. This can have implications on mortality and morbidity associated with anesthetic complications during DBS implantation (Seller e.a. 2003). Therefore, a thorough pre-operative anesthetic assessment and evaluation is required to assist the planning of safe peri-operative care. Patients should be rehydrated adequately and any deranged electrolyte levels should be corrected pre-operatively. There is an increased risk of intra-operative hypothermia. Therefore measures should be taken to keep the patient warm during surgery. Doses of most (anesthetic) drugs should be adjusted for weight. Patients are particularly susceptible to nerve palsies due to their cachexia and loss of cushioning subcutaneous tissue. Therefore they

must be placed carefully on the operating table. During the operation, ECG-changes and potassium levels should be monitored carefully to minimize the risk of arrhythmias (Seller e.a. 2003). To minimize the overall increased risks associated with anesthesia the weight and somatic condition will be maximally optimized prior to surgery.

In case of the hypothesized weight gain following successful treatment with DBS, there is a risk of development of a refeeding syndrome (Khan e.a. 2010). The refeeding syndrome is a potentially lethal complication of refeeding in patients that are severely malnourished. Features of the refeeding syndrome are: salt and water retention leading to oedema and cardiac failure; hypokaliaemia; hypophosphataemia; rapid depletion of thiamine leading to Wernicke*s encephalopathy and/or cardiomyopathy; hypomagnesaemia. Especially rapid and excessive refeeding imposes a risk for development of the refeeding syndrome. It is expected that weight increase following treatment with DBS will be gradual rather than sudden and excessive. Other DBS studies, for example in OCD and depression, showed that improvement of symptoms takes several months (Denys e.a. 2009; Greenberg e.a. 2010; Lipsman e.a. 2013; Schlaepfer e.a. 2008). However, patients are advised to increase their food intake gradually and under supervision of a dietary consultant. The somatic condition and the potential development of a refeeding syndrome will be closely monitored by a physician. Regular physical examinations and laboratory tests will be conducted. If necessary, patients can be admitted to the Psychiatric Medical Unit of the AMC.

Lipsman e.a. (2013) reported several adverse events in their pilot study on DBS in AN, with one serious DBS-related adverse event (seizure during programming) and the other serious adverse events being related to the underlying illness. One patient in this study developed hypophospataemia and a refeeding delirium (Lipsman e.a. 2013).

The fMRI assessment will be conducted in accordance with established guidelines for MR imaging in DBS. In particular, care will be taken to minimize heat production in the vicinity of the DBS electrodes. Therefore, MR imaging will be performed on a 1.5 Tesla system rather than a 3 Tesla system. Moreover, we will employ low Specific Absorption Rate (SAR) sequences and use MR paradigms known to produce robust activations to limit scanning time (Carmichael e.a. 2007, Bhidayasiri e.a. 2005, Georgi e.a. 2004).
As stated before, the subjects of this study are patients with very severe, chronic, treatment refractory AN, associated with poor outcome and a high mortality, for who there are no further treatment options. With this pilot study, we aim to provide an optimal balance between risk and opportunity.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria studypopulation:
• Primary diagnosis: Anorexia Nervosa (restricting or purging type; 307.1) according to the DSM-IV criteria based on a psychiatric interview
• Chronicity, defined by an illness duration > 10 years
• Disabling severity with substantial functional impairment according to the DSM-IV criterion C and a Global Assessment of Function (GAF) score of 45 or less for at least two years
• Treatment refractoriness, defined as lack of response to two or more typical modes of treatment , including one hospital admission or inpatient treatment in a specialized clinic, as described in the Multidisciplinaire Richtlijn Eetstoornissen (Trimbosinstituut 2008).
• BMI < 15 (level of severity acoording to the DSM 5: extreme)
• Age: 25-65 years old
• Written informed consent

• Dutch or English speaking and able to answer the study questions
• Able to fully understand the consequences of the procedure
• Capable to make his or her own choice without coercion ;Inclusion criteria healthy controlgroup EEG-substudy:
1. Female
2. 25-50 years
3. Matched intelligence level (NLV/DART)
4. Healthy BMI (18.5-25)

Exclusion criteria

Exclusion criteria studypopulation:
• Unstable physical condition (severe electrolyte disturbances, cardiac failure, other physical contraindications for surgery/anesthesia). The use of anticoagulants must be able to be stopped before surgery
• Treatable underlying cause of anorexia/underweight
• Active neurological disease like Parkinson*s disease, dementia, epilepsy
• Schizophrenia/history of psychosis, bipolar disorder
• Alcohol or substance abuse (including benzodiazepines) during last 6 months
• Current Tic disorder
• Antisocial personality disorder
• Standard MRI scan exclusion criteria (pregnancy, pacemaker and metals contraindicated for MRI);Exclusion criteria healthy control group EEG-substudy:
1. (History of) eating disorders
2. (History of) psychiatric disorders
3. Relevant somatic/neurological disorders
4. Use of psychoactive drugs/substances

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-02-2016
Enrollment:	24
Type:	Actual

Medical products/devices used

Generic name:	Neurostimulator Activa PC
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO Date:	20-05-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL40930.018.12

Study results

Date completed:	05-06-2020
Results posted:	19-08-2022
Actual enrolment:	4

First publication
19-08-2022