

Neuromodulation Treatment for Anorexia Nervosa: A Brief Review



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Abstract

To date, three different neuromodulation techniques have been used to treat a total of 154 patients with anorexia nervosa. In the present review, we describe these techniques and the treatment outcomes reported in the relevant literature. Although the reported results are good overall, the results must be interpreted cautiously due to the heterogeneity of this disorder and the limitations (methodology, sample sizes) of those studies.

Keywords: Anorexia Nervosa; Neuromodulation; Deep Brain stimulation; Transcranial Magnetic Stimulation; Transcranial Current Direct Stimulation

Abbreviations: AN: Anorexia Nervosa; BMI: Body Mass Index; DBS: Deep Brain Stimulation; DLPFC: Dorsolateral Prefrontal Cortex; MD: Major Depression; NAcc: Nucleus Accumbens; OCD: Obsessive Compulsive Disorder; RCP: Randomized Controlled Trial; SGC: Subgenual Cingulate; TDCS: Transcranial Direct Current Stimulation; TMS: Transcranial Magnetic Stimulation

Introduction

Anorexia Nervosa (AN) is the most important eating disorder, with a prevalence ranging from 0.7%-3%. In addition to the central symptoms of the disorder, a large proportion of these patients also present comorbid psychopathology, including with high rates of comorbid mental disorders. Of all mental disorders, AN is associated with has the highest rates of morbidity and mortality rates of all mental disorders. Approximately 20% of patients are resistant to conventional treatment. Although the precise causes of this disorder are not fully well-understood, it is widely believed to be a multifactorial disorder, including genetic, personality, environmental, and neurobiological factors [1,2]. The neurobiological component likely in particular is believed to plays a major role in the development of AN. Several different hypotheses related to this factor have been proposed to explain the underlying neurobiological pathophysiology of AN. The most widely accepted hypothesis is a dysfunctional cortico-limbic dysfunction system leading to alterations in the regulation of food-related emotions, rewards, and behaviors [2,3]. Based on data from imaging studies indicate that, the

brain regions most closely areas involved in the pathophysiology of this disorder are the insula, the parietal cortex, the anterior and Subgenual Cingulate (SGC), the ventral striatum (Nucleus Accumbens; NAcc), and the left dorsolateral prefrontal cortex (DLPFC) [3]. In recent years, there has been a growing interest in identifying and offering non-pharmacological alternatives to patients with treat mental illnesses that fail to do not respond to conventional treatment. One such approach is neuromodulation, which encompasses several different techniques by in which brain function is stimulated or inhibited by specific techniques, without damaging the brain tissue. These such techniques are classified as invasive if they require surgery or non-invasive if they can be applied externally, without surgery [4,5].

The aim of the present review article is to review the various approaches in neuromodulation that are currently carrying out for AN patients treatment.

Neuromodulation technique and results

To perform the review, we searched the Medline and Scopus databases using the following key words: Anorexia nervosa,

neuromodulation. This search identified (18 articles), and three different types of Neuromodulation techniques have been applied in patients with AN, including:

- a) Deep brain stimulation (DBS),
- b) Transcranial magnetic stimulation (TMS), and
- c) Transcranial current direct stimulation (tDCS).

Below we describe each technique and the evidence base to support their clinical use in the treatment of AN. There is currently no approval for any neuromodulation technique (neither by the FDA nor by the CE marking) for AN patients.

DBS

DBS is an invasive stimulation technique in which two electrodes (generally 4 contacts/electrode) are inserted bilaterally in deep areas of the brain using a stereotactic technique. The electrodes are connected to an internal pulse generator, which is inserted subcutaneously. This generator sends electrical impulses to the electrodes. Although the precise mechanism of action is not well-understood, DBS is believed to act by inhibiting a malfunctioning brain circuit. Currently, the only mental illness for which DBS has been approved (FDA and CE marking) is Obsessive Compulsive Disorder (OCD). Our literature search identified a total of nine publications (26 patients), as follows: four case reports, two case series, two clinical trials and one clinical trial protocol publication. Overall, 26 patients with AN have been treated by DBS. In these studies, three different brain sites have been targeted: the SGC, the NAcc, and the Bed Nucleus of the Stria Terminalis (BNST) [6-11].

DBS to the SGC

Of the nine studies, three applied to DBS to the SGC. In one study—a case report by Israel et al. [12] DBS was administered to a patient with Major Depression (MD) and comorbid an with a Body Mass Index (BMI) of 19.65. In that patient, DBS was applied unilaterally using an intermittent approach (130 Hz, 91 ms, 5 mA mp). At 30 months of follow-up, the patient successfully maintained BMI [12]. In the year [9]. reported initial results from a pilot clinical trial involving six patients with chronic AN and DBS in SGC (follow-up 9 months). Four of the six patients had good response to DBS. That trial was subsequently expanded to 16 patients (including the original six), with results reported in 2017. The larger trial also had a longer follow-up (one year). The DBS parameters were 130 Hz, 90 ms, 5-6 V. Numerous different variables were assessed, including BMI, psychometric measures, Quality of Life (QoL), and imaging data obtained by fluorodeoxyglucose-positron emission tomography (FDG-PET). All 16 patients in that trial showed improvement, including the patients who had not responded at 9 months, in BMI, psychometric results and QoL. In addition, all of the patients presented changes in cerebral metabolism at 6 months. Complications included the following: epileptic seizure (n=1),

surgical wound infection (n=1), worsening mood (n=1), air embolism (n=1), and pain (n=5) [8,9,13].

DBS to the NAcc / ventral striatum

The first reported case of a patient with AN treated with DBS to the ventral striatum was published in 2013 by McLaughlin et al. [11]. The patient (BMI, 18.5), who had OCD and comorbi AN, received DBS (120 Hz, 120 ms, 7.5 V) to the ventral striatum, which resulted in a modest increase in BMI, from 18.5 to 19 [11]. In that same year, Wang et al, [6] performed DBS in two adolescents (BMI \leq 13). The stimulation parameters were 2.5-3.8 V, 135-185 Hz, 120-210 ms to the NAcc. At 12 months of follow-up, the patients had no complications and showed improvement in BMI values, psychometric measures, and [6]. In another case series, Wu et al. [7] performed DBS in four adolescents (BMI < 13) using the following DBS stimulation parameters: 180 Hz, 90 micro sg. Follow-up ranged from 9-50 months. All patients gained a mean of 65% of body weight (BMI,) [17-22] together with significant improvement in psychometric measures, with no complications [7]. Recently, Park et al. [14] published a protocol for a clinical trial involving six patients with chronic AN and comorbid OCD. That trial includes a double-blind phase with image evaluation by magnetoencephalography. The planned follow-up after DBS is 13 months. Results are pending [14].

DBS to the BNST

Blomsted et al. [10] described a patient with MD and comorbid AN. The DBS parameters were 130 Hz, 120 ms, 4.3 V. At 12 months of follow up, although there was no improvement in BMI, they did observe a reduction in food-related anxiety [10]. In Manuelli et al, [13] described a patient who underwent DBS to the BNST (parameters: 130 Hz, 4V, 60 ms). The patient's mean BMI increased from 16.3 (baseline) to 18.98 at 6 months post-DBS [13-20].

TMS

TMS is a technique in which a magnetic field is generated through a coil placed on the skull. The electrical current that is generated penetrates the skull to depolarize the neurons in the tissue located immediately below the coil. Depending on the parameters used, the cortex can either be stimulated (> 1 Hz) or inhibited (< 1 Hz). A repeated TMS technique (rTMS) with a low frequency is commonly used. The duration of the immediate effects on the brain is short. We identified a total of seven studies (111 patients) describing the use of this technique to treat AN, as follows: one case report, two case series, one trial protocol, and three clinical trials. The stimulation target was the same (left DLPFC) in all seven studies. The first report, published by [21], described the case of a 24-year old patient with AN and comorbid depression. The treatment protocol consisted of 41 sessions of TMS at 10 Hz with 2000 pulses. At 3 months of follow-up, the patient's BMI increased from 12.4 to 16 [21]. In published the results of a pilot study involving 10 patients with AN (age range,

18-44 years). Treatment consisted of a single session of 10 Hz (10000 pulses). Although BMI did not increase, a reduction was observed in levels of feeling full, fat, and anxious [19].

In that same year, McClelland et al, [17] reported one-month results from two patients treated with TMS for AN. The treatment protocol was 20 sessions of high frequency pulses. Although BMI did not improve, central symptoms of AN and mood improved in both patients [17]. Barholdy et al, [20] published a clinical trial protocol (TIARA, randomized trial) for a study involving 44 patients with chronic (>3 years of duration) AN. The treatment protocol called for 20 high frequency sessions. Outcome measures include BMI, psychopathology, central symptoms of AN, QoL, and neuroimaging data. Results are pending. In [16], McClelland et al, [15] reported results from a study involving 5 patients with AN (age range, 23-52 years). The treatment protocol was 10,000 pulses in 20 sessions (20 min/session). At 12 months of follow-up, the patients had lost weight, but both affective and central symptoms of the disorder had improved. In that same year, the same authors [16] reported results from a Randomized Controlled Trial (RCT) involving 49 patients who underwent TMS (treatment protocol: single 20-minute session at 10 Hz, 100,000 pulses).

However, they observed no significant improvement in symptoms of depression or anxiety, and only a modest improvement in central symptoms of the disorder [17]. Jassova et al, [22] described the case of a patient who received 10 days of TMS (10 Hz, 15 steps/day 100 pulses/train); unfortunately, there was no improvement in any of the disorder-related factors [22]. Finally, Dalton et al. [18] conducted an RCT comprising 34 patients diagnosed with chronic (> 3 years duration) AN. The protocol consisted of 20 sessions of daily TMS over 4 weeks. At 4 months of follow up, BMI and central symptoms were virtually unchanged; however, there was a moderate improvement in QoL and a marked improvement in mood.

tDCS

TDCS is a technique in which two surface electrodes are placed on the scalp. A weak electrical current is then applied to the scalp to restore the neuronal excitability of the underlying cortex. The effect can be excitatory or inhibitory, depending on whether the anode or cathode is used to deliver the current. The duration of the immediate effects on the brain are short.

Two studies involving a total of 17 patients have been reported to date, both targeting the left DLPFC. In Khedr et al, [23] reported results from a series of 7 patients with AN (age range, 16-39 years). The treatment protocol was 2 mA mp, anodal, 10 sessions of 25 minutes for 10 days. At one month of follow up, three of the seven patients showed improvement in central symptoms of AN and mood. Strumila et al, [24] recently reported the results of a clinical trial (STAR study) involving 10 patients. In that trial, the treatment protocol was an anode current to the left DLPFC and a cathode to the right DLPFC. The

treatment consisted of 20 sessions of 2 mAM twice daily (20 min/application) for 23 weeks, twice daily, resulting in significant improvements in central symptoms of AN and mood [24].

Conclusion

Currently, a wide range of neuromodulation techniques are under investigation for the treatment of refractory AN. Due to the non-invasive nature of TMS and tDCS, it is possible to evaluate a larger number of patients. However, these techniques have important limitations, mainly that the duration of the effects of treatment is limited and targets located deep within the brain cannot be reached. By contrast, although DBS is invasive and expensive, the results can be maintained over a longer period of time, and a wide range of brain regions can be targeted for neuromodulation.

To date, RCTs have been performed only with TMS, and those trials did not yield any improvement in BMI, with little to no effect on symptoms. Given the relative lack of RCTs in this area, together with the wide heterogeneity of the disorder (type and severity, associated comorbidities) and important differences in study design (e.g., chronic versus non-chronic patients, stimulation targets, outcome measures) and the small sample size of these studies, it is difficult to draw any definitive conclusions about the efficacy of neuromodulation as a treatment for AN. Despite the aforementioned limitations in the evidence base, the results reported to date are generally positive and encouraging. However, more data are needed, preferably from large RCTs.

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Conflict of Interest

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