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Review Article

The utility of deep brain stimulation surgery for treating eating disorders: A systematic review

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ABSTRACT

Background: Deep brain stimulation (DBS) has demonstrated preliminary success as a treatment for neuropsychological disorders including obsessive-compulsive disorder and substance use disorder. This systematic review aims to assess the use of DBS in treating eating disorders (EDs) to determine its utility and the extent of adverse effects.

Methods: A PubMed search following PRISMA guidelines was executed to find studies encompassing DBS as a treatment of ED. Outcomes were extracted from the literature and summarized while a review of quality was also performed.

Results: From a search yielding 299 publications, 11 studies published between 2010 and 2020 were found to fit the inclusion criteria. Out of 53 patients who began with an abnormal BMI before treatment, 22 patients (41.5%) achieved normal BMI on follow-up. Significant neuropsychological improvement was seen in most patients as measured by neuropsychiatric testing and questionnaires.

Conclusion: DBS as a treatment for ED may result in significant objective and psychological benefits. Further studies should aim to increase the sample size, standardize follow-up protocol, and standardize the neuropsychiatric tests used to determine psychological and physiological benefits.

Keywords: Anorexia nervosa, Deep brain stimulation, Neuromodulation, Obesity, Systematic review

INTRODUCTION

Eating disorders (EDs) encompass psychiatric illnesses which manifest as disruptions or severe alterations in a person's eating behavior. Incidence is more common in women between the age of 15 and 35 years old and end complications may lead to long-term comorbidities such as high cholesterol, heart disease, and diabetes.[34] Current practices in the initial steps to treat ED are any combination of weight management, appetite suppression, pharmacotherapy, and psychotherapy.[7,36,45] Despite these treatments achieving remission in a selection of patients, many remain refractory and require further treatment. This presents a need for further interventions to prevent harm to patients who are otherwise left untreated. Current surgical procedures used to treat ED include gastric bypass, brain lobe resections, and radiofrequency ablation.[25] Deep brain stimulation (DBS) has recently been introduced as a potential treatment for ED and has demonstrated preliminary success.[27,29]

DBS is a neurosurgical procedure in which electrodes stimulate targeted brain regions to alter or modulate neural circuitry.[30] Clinical application of DBS has already been successfully implemented to treat Parkinson's disease and refractory seizures, and there has also been demonstrated preliminary success for the treatment of obsessive-compulsive disorder (OCD), tremor, and substance use disorder (SUD). There are several reported complications that are typical of neurosurgical procedures including infection, hemorrhage, and neurologic deficit.[19,37] Although there are reported adverse effects resulting from electrode stimulation, DBS has the benefit of being reversible and the stimulation leads can be repositioned through revision procedures.[37] Adjustable stimulation parameters include voltage, pulse width, frequency, specific coordinates, and number of electrodes, which may be adjusted to optimize success of the procedure.[9]

The literature remains unclear as to which circuits and brain regions should be stimulated with DBS. The nucleus accumbens (NAc) has been linked to obesity[16] and the frontobasal ganglia-thalamic pathway is associated with obesity and anorexia nervosa (AN).[32] Recent pilot studies targeting the NAc with DBS to treat AN have shown preliminary success in its utility to treat refractory cases, potentially through modulating neural circuits involved in metabolic function.[29,47] Similarly, NAc DBS stimulation has achieved body mass index reductions indicative of improvement of pathological obesity through potential links in cravings circuitry.[16]

This study aims to systematically review and assess the current literature regarding the use of DBS to treat ED when typical noninvasive therapies fail. These findings further describe the utility of DBS as a treatment in refractory ED patients and identify adverse effects to consider when deciding on treatment options. A meta-analysis construct was not pursued because of limitations including small sample size, heterogeneity of outcome measures, and case report/series comprising the majority of the found literature.

METHODS

Search strategy

PRISMA guidelines were followed to conduct the systematic review. A literature search of the PubMed database included all publications in English that use human subjects from earliest records to June 2020 using the search formula: ("deep brain stimulation" OR DBS) AND ("eating disorder*" OR bulimi* OR anorex* OR obese OR obesity OR binge OR "food intake disorder" OR "feeding disorder").

Inclusion and exclusion criteria

Two independent reviewers performed an initial screening protocol and removed any publications that were duplicates, not in English, not published in a peer-reviewed journal, abstracts-only, or did not use human subjects. Afterward, the reviewers screened the remaining publications for eligibility based on the inclusion criteria: DBS must be the primary intervention; main findings pertain to an ED; study is a clinical trial, case report, or case series. In the case of disagreement, a third reviewer made the decision after reviewing the study. The process of study selection is summarized in [Figure 1].

Quality assessment

Two independent reviewers assessed the quality of each publication in accordance with the MINORS quality assessment tool [Table 1].[38] Each publication was reviewed and assigned a score of 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate) for each criterion, and the individual score of each criterion was subsequently summed together to generate an overall score for each study. The ideal score is 10. A third reviewer decided the final score in the case of disagreement after reviewing the study.

Measure of patient outcome

For the purpose of this study and to present data with more homogeneity, treatment success was determined based on CDC suggested guidelines of a healthy BMI range, in which patients in studies were assessed for the reported BMI's before and after surgery. Therapeutic outcomes were determined based on reports of successful treatment of AN symptoms, attenuation of a normal menstrual cycle, decrease in binge behavior, performance on neuropsychological tests, and metabolic rate changes. Adverse effects were identified and recorded when available.

Table 1: MINORS quality assessment (ideal score=10).

Publications	Total score
Liu *et al.*, 2020	8
Weichart *et al.*, 2020	8
Manuelli *et al.*, 2019	7
Whiting *et al.*, 2019	8
Blomstedt *et al.*, 2017	6
Lipsman *et al.*, 2017	6
Harat *et al.*, 2016	6
Zhang *et al.*, 2013	8
Whiting *et al.*, 2013	9
Lipsman *et al.*, 2013	8
McLaughlin *et al.*, 2013	5
Wu *et al.*, 2013	7
Israël *et al.*, 2010	4

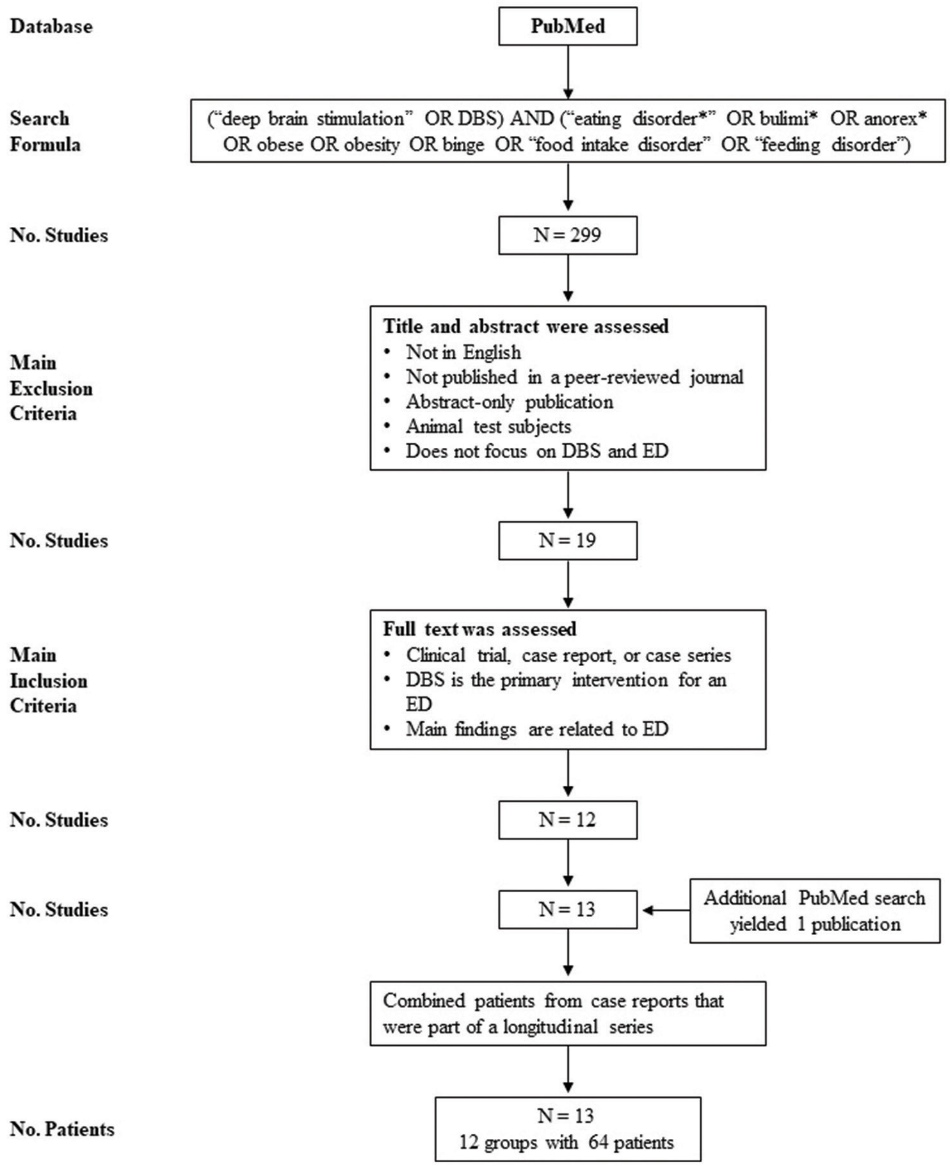

Figure 1: Flowchart depicts selection process for publications, number of publications (N), deep brain stimulation (DBS), eating disorders (ED)

RESULTS

Summary of findings and patient demographics

The EDs treated with DBS reported in the literature include AN and obesity.[3,16,22,27-29,31,32,41,43,44,46,47] Despite the inclusion of bulimi* in our preliminary search for papers, no studies on DBS for bulimia met the inclusion criteria. The most common cooccurring conditions included OCD, major depressive disorder, and anxiety disorders. There was a total of 63 female patients and 1 male patient with ages ranging from 16 to 60 years old. Of those patients, five were lost to follow up. Follow-up times ranged from 6 to 50 months. Cooccurring conditions, follow-up times, and total number of patients at follow-up are summarized in [Table 2].

Reports of treatment success

The CDC suggests that a healthy BMI ranges from 18.5 to 24.9.[6] BMI was reported for a total of 59 patients, 2 of which were within the healthy range at baseline and 4 of which only had BMI recorded for 1-month postsurgery.[22,32,47] Of the remaining 53 patients, 42.3% (22/53) achieved a BMI within the healthy range at the end of their respective follow-up period, which ranged from 6 to 39 months.[3,16,27,29,31,41,44,46] When comparing success rates in treating AN and obesity, 45.8% (22/48) of AN

Table 2: Summary of case reports and series of DBS for ED.

Publications	Condition	Other conditions	Target	Stimulation parameters			Follow-up time (months)	# of patients (excluding lost to follow-up)	BMI in healthy range post-DBS (%)
				Hertz	µsec	V/mA			
Liu *et al.*, 2020	Anorexia nervosa	12 MDD, 9 OCD, 7 severe anxiety	Nucleus accumbens	160–180	120–150	2.5–4.0 V	24	28	42.8
Weichart *et al.*, 2020	Obesity	None specified	Nucleus accumbens	130	120	3.5–5.0 V	30	1	0
Manuelli *et al.*, 2019	Anorexia nervosa	None specified	BNST	130	60	4.0 V	6	1	100
Whiting *et al.*, 2019 Whiting *et al.*, 2013	Obesity	2 HTN, 1 sleep apnea, 1 DM2, 1 migraine, 1 LE edema	Lateral hypothalamic area	60–250	60–120	1.0–7.0 V	30–39	3	0
Blomstedt *et al.*, 2017	Anorexia nervosa	MDD	MFB, BNST	130	60	3.0 V	48	1	0
Lipsman *et al.*, 2017 Lipsman *et al.*, 2013	Anorexia nervosa	12 MDD, 10 PTSD, 6 OCD, 3 GAD, 2 anxiety, 1 SUD (remission), 2 BPD	Subcallosal cingulate	130	90	2.5–7.0 V	9–12	14	42.9
Harat *et al.*, 2016	Obesity	Damaged hypothalamus, glucose intolerance, lumbar spondylosis, mild depression	Nucleus accumbens	130	208	3.75 mA	14	1	0
Zhang *et al.*, 2013	Anorexia nervosa	None specified	Nucleus accumbens	-	-	-	6	4	0
McLaughlin *et al.*, 2013	Anorexia nervosa	OCD, MDD, GAD, ADHD	Ventral capsule/ventral striatum	120	120	7.5 V	36–48	1	100*
Wu *et al.*, 2013	Anorexia nervosa	3 OCD, 1 GAD	Subgenual cingulate cortex	-	-	-	36	4	75
Israël *et al.*, 2010	Anorexia nervosa	MDD	Nucleus accumbens	130	91	5 mA	9–50	1	100*

*BMI was in healthy range pre-DBS. OCD: Obsessive compulsive disorder, MDD: Major depressive disorder, HTN: Hypertension, DM2: Diabetes mellitus type 2, GAD: Generalized anxiety disorder, ADHD: Attention-deficit hyperactivity disorder, PTSD: Posttraumatic stress syndrome, SUD: Substance use disorder, BPD: Borderline personality disorder patients achieved a BMI in the healthy range compared to 0% (0/48) of obesity patients.[3,16,22,27,29,31,32,41,44,46,47]

Therapeutic outcomes

All therapeutic outcomes and adverse effects are outlined in [Table 3]. A total of eight studies used DBS to treat AN and three used DBS to treat obesity. BMI was used in all studies to measure treatment success along with neuropsychiatric tests and psychosocial metrics. In two studies, glucose metabolism in the brain was measured by positron emission tomography (PET) standardized uptake.[27,28,47] One study also used body composition to evaluate treatment efficacy.[31]

About 87.5% (7/8)[22,27-29,31,32,46,47] of studies treating AN symptoms reported increases in BMI at follow-up; however, one patient showed a decrease in BMI.[3] Normal mean BMI was achieved at the final follow-up in five out of the eight studies.[22,29,31,32,46] Body composition study showed increased body cell mass, resting energy expenditure, and daily intake post-DBS in one patient.[31] Menstrual cycles were restored in five patients.[31,46] Food intake was reported to be more stable and there was reduced vomiting in one patient.[3] Decreased metabolic activity was seen in the frontal cortical regions, cerebellum, and posterior cortical regions posttreatment as measured by PET standardized uptake in two studies.[27,28,47]

Significant decrease in BMI was seen in all obesity-related studies[16,41,43,44] except for in one patient;[44] however, none of the BMI's entered a healthy range posttreatment. Although one study did not observe significant decreases in BMI, they reported increases in resting metabolic rate and sleeping energy expenditure during DBS treatment.[43] Furthermore, they reported decreased urge to eat which was observed in three patients, however, binge eating behavior and dieting skills only improved in one of these patients.[44] Reaction times and prefrontal cortex connectivity improved during treatment in one study.[41] One patient had increased food cravings and an increase in her BMI during periods of no treatment (OFF periods), but her symptoms and BMI improved after resuming DBS.[16]

Neuropsychological testing

Of the 11 included studies, only one study did not use any neuropsychological testing or questionnaires.[41] Administered tests included Hamilton Anxiety Rating Scale (HAMA), Hamilton Depression Rating Scale (HAMD), Social Disability Screening Schedule (SDSS), Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Eating Attitudes Test (EAT-26), cognitive neuropsychology tests, mean quality of life, and questionnaires regarding the patient's attitude toward food.

Three studies reported improvement of mood, anxiety, depression, and social functioning as represented by a mean decrease in Y-BOCS, HAMA, HAMD, and SDSS scores, respectively.[27-29,46] Improvement in anxiety and quality of life was only seen in patients with significant changes in BMI.[28] Purging behaviors decreased in 57.1% (8/14) of patients and abstinence was achieved in 28.6% (4/14) of patients.[27] In one patient, AN symptoms, including "food phobia," improved on all psychosocial metrics.[31] Mood and anxiety concerning food and eating vanished in one patient after the procedure.[3] EAT-26 score decreased dramatically in one patient after DBS treatment and reflected in her ability to maintain a normal BMI for 3 years.[22] There was demonstrated improvement in visual-spatial working memory but also a slight decrease in executive function in one patient.[16]

Adverse effects

The most common adverse effects were nausea, pain, and infection at the incision site.[27-29,43,44,47] Other acute adverse effects included hot flashes, flushing, and sweating.[29,43,44] Some serious adverse effects in three separate patients included gas embolism, panic attacks, and seizures.[28] One study reported a decrease in BMI as an adverse effect.[3] One patient had her device explanted at 18 months due to rejection and two patients had the device explanted for unclear reasons.[27,29] No adverse effects were reported in 18.2% (2/11) of studies,[16,46] while 36.4% (4/11) of studies did not discuss or report adverse effects.[22,31,32,41]

Coordinates and stimulation parameters

Coordinates and stimulation parameters are summarized in [Table 2]. The reported brain regions stimulated in anorexia patients in the studies included the NAc (3/8),[22,29,47] bed nucleus of stria terminalis (2/8),[3,31] medial forebrain bundle (1/8),[3] subcallosal cingulate (1/8),[27,28] ventral capsule/ventral striatum (1/8),[32] and subgenual cingulate cortex (1/8).[46] The brain regions stimulated in obesity patients were the NAc (2/3)[16,41] and lateral hypothalamic area (1/3).[42,43] Only 45.5% (5/11) of studies reported coordinates for lead placement.[29,31,41,43,44,46] Methods of lead placement included frame-based and MRI-guided stereotactic procedures as well as the use of X-ray and intraoperative CT-MRI fusion, and 81.8% (9/11)[3,22,27-29,32,41,43,44,46,47] of studies confirmed placements of electrodes postoperatively while 18.2% (2/11)[16,31] used intraoperative confirmation instead. The stimulation parameters were reported in 81.8% (9/11)[3,16,22,27-29,31,32,41,44] of studies and ranged from 120 to 250 Hertz, 60–210 μs, and 2.5–7.5 volts. Two studies reported stimulation in milliamps instead of volts with recordings of 3.75 mA and 5 mA.[16,22]

DISCUSSION

Neurosurgical treatment of ED is a recent development with potential to benefit patients who are refractory to other

Table 3: Summary of reported treatment outcomes and adverse effects.

Publications	Condition	Treatment outcome	Adverse effects
Liu *et al.*, 2020	Anorexia nervosa	BMI significantly increased at both 6-month and 1-year follow-ups with 12 of the 19 patients achieving normal BMI of above 18.5 at 2 years. Mood, anxiety, and depression symptoms decreased as measured by a significant improvement in Y-BOCS, HAMA, and HAMD scores at 6-month and 2-year follow-ups. Increased social functioning at 2-year follow-up was demonstrated by improved SDSS scores	Transient pain at incision site, flushing and sweating, 1 patient had device explanted at 18 months due to device rejection
Weichart *et al.*, 2020	Obesity	BMI decreased from 55.8 to 39.3 over 36 months of treatment with a total of 98.8 lbs. lost. Reaction times and connectivity in dorsolateral and dorsomedial prefrontal cortex improved during phase of optimal stimulation	-
Manuelli *et al.*, 2019	Anorexia nervosa	Significantly increased BMI from 16.31 to 18.98, body cell mass, resting energy expenditure, and daily intake at 6-month follow-up. Symptoms of AN improved on all psychosocial metrics with reduction of "food phobia," restoration of menstrual cycle at 4 months post-DBS, and no signs of refeeding syndrome seen during follow-up examinations	-
Whiting *et al.*, 2019 Whiting *et al.*, 2013	Obesity	20% increase in RMR and 10.5% increase in SEE in patient 1, 16% increase in RMR and 4.8% increase in SEE in patient 2 during optimal stimulation. After augmentation of RMR by LHA DBS, significant weight loss was seen in 2/3 patients. Reduced binge eating in 1/3 patients and improved diet skills in 1/3 patients. Decreased urge to eat was observed in all patients after long-term programming at the RMR optimized setting	Nausea, anxiety, hot flashes, flushing
Blomstedt *et al.*, 2017	Anorexia nervosa	Decreases in BMI were not statistically significant (BMI decreased from 16.2 to 15.2 at 24-month follow-up after first surgery and decreased to 14.3 at 12-month follow-up after second surgery). After the second procedure, anxiety concerning food and eating vanished, patient stopped vomiting, and food intake became more stable	BMI decreased
Lipsman *et al.*, 2017 Lipsman *et al.*, 2013	Anorexia nervosa	On 6-month follow-up, mean quality of life score increased in three patients with improved BMIs. Mean BMI increased from 13.83 to 17.34 on 12-month follow-up and purging behaviors decreased in 8/14 patients with 4/14 showing complete abstinence. Depression, mood, and anxiety symptoms decreased as shown by improved mean YBOCS and HAMD scores. Voxel-wise analyses of PET scan show decreased metabolism in frontal regions and cerebellum and increased metabolism in posterior cortical regions and parietal regions	Pain and/or infection at incision site, nausea, seizure, panic attacks, air embolism, two patients had the device explanted due to unclear reasons
Harat *et al.*, 2016	Obesity	BMI decreased from 52.9 to 46.2 and weight decreased from 151.4 kg to 132 kg after 3 months, weight increased again to 142 kg after 9 months, and then weight decreased to 137 kg after 14 months. Increased food craving during switch-off periods. No evidence of depressive syndrome at final follow-up. Cognitive neuropsychology test results showed gradual improvement in visual-spatial working memory but showed that efficiency of executive functions decreased slightly but were within normal limits	No adverse effects reported

(*Contd...*)

Table 3: (*Continued*)

Publications	Condition	Treatment outcome	Adverse effects
Zhang *et al*., 2013	Anorexia nervosa	4/6 patients underwent DBS and BMI increased at 1-month follow-up for all four patients. Hypermetabolism and increase in glucose metabolism is seen in frontal lobe, limbic lobe, right claustrum, left subcallosal gyrus, bilateral lentiform nucleus, left insula, and brainstem in AN patients compared to healthy controls at baseline. After NAcc-DBS, glucose metabolism decreased in the frontal lobe, bilateral lentiform nucleus, and hippocampus in AN patients	Pain and/or infection at incision site, nausea
McLaughlin *et al*., 2013	Anorexia nervosa	BMI increased from 18.5 to 18.9–19.6 during follow-ups. Patient-reported "different" feelings toward food were less bothered by what she ate, and even ate sweets/candy, which she avoided prior to surgery. When contact with ventral caudate was turned on, anxiety, mood, and OCD symptoms worsened, and she decreased in weight. After this was turned off, the patient gained another 4 lbs. and her symptoms improved	-
Wu *et al*., 2013	Anorexia nervosa	Average BMI at follow-up was 19.6 with an average 65% increase in body weight. Y-BOCS and HAM-A scored reduced to 1.7 and 2. All patients no longer met criteria for AN and menstrual cycle was restored in all patients at around 7 months postsurgery. 3/4 patients were able to continue school education	No adverse effects reported
Israël *et al*., 2010	Anorexia nervosa	BMI was 18.2 after the second DBS treatment. EAT-26 score decreased from 40.56 to 12.48 after second DBS treatment and to 1.04 and 1 at 2- and 3-year follow-up, respectively. Patient did not need further interventions and has maintained an average BMI of 19.1	-

BMI: Body mass index, RMR: Resting metabolic rate, SEE: Sleep energy expenditure, HAM-A: Hamilton Anxiety Rating Scale, HAMD: Hamilton Depression Rating Scale, SDSS: Social Disability Screening Schedule, Y-BOCS: Yale-Brown Obsessive Compulsive Scale, EAT-26: Eating Attitudes Test

current treatment options. Furthermore, combined treatment plans may enhance treatment efficacy and potentially reduce morbidity. Larger studies investigating the influence of the patient population, neurobiological mechanisms, and limitations are necessary for transition to standard clinical application of DBS to treat ED.

Patient population

OCD was a common concomitant neuropsychiatric disorder among patients with AN. OCD is characterized by obsession and compulsions that are either time consuming or cause significant psychological distress.[1] Estimates suggest that between 35 and 44% of individuals with AN also meet criteria for OCD.[26] This is consistent with the patient population in the studies, in which 35% (17/48) of patients treated for AN were also diagnosed with OCD. Multiple studies have reported DBSs success in treating OCD with significant reductions in YBOCS scores.[4] Prior studies on DBS for OCD have shown that 60% of patients had 35% reduction in symptoms as measure by YBOCS scores with an average decrease of 45%.[2] This shows that the relationship between AN and OCD between patients influences efficacy. We suggest for future studies investigating DBSs role as a treatment for AN to exclude patients with concomitant OCD, or have a large enough sample size to have a significant number of patients without concomitant psychiatric disorders that may be grouped in analysis to better isolate the efficacy of DBS for AN treatment.

The most common concurrent condition in patients with obesity who underwent DBS treatment was hypertension (HTN).[43,44] This may be influenced by the well-established relationships between obesity and HTN or patient age across studies since HTN is more likely to afflict older patients and those with increased body habitus. The average age of obesity patients was two decades older than that of the AN patients which may have influenced the range of concomitant conditions.

Only one male was represented across studies, which is a potential limitation to the current literature on DBS for ED.[44] AN is estimated to affect females at 3 times the rate of males, with lifetime prevalence at 0.9% compared to 0.3%, respectively.[21] However, obesity rates are reported to be the same among men and women.[12] Inclusion of male participants in future studies should be done to determine if there is also a gender dependent difference in treatment efficacy of DBS for ED.

Therapeutic potential of DBS to treat ED

The three essential diagnostic criteria for AN as described in the DSM-V should be considered when treatment plans are being generated for patients. These include the restriction of energy intake relative to requirements, intense fear of gaining weight or of becoming fat, and persistent behavior that interferes with weight gain even at a significantly low weight.[1] BMI is noted as a useful tool for the diagnosis of AN as it may represent significantly low weight, which is defined as weight less than minimally normal.[1]

Current treatment of AN relies on a multimodal approach that combines pharmacotherapy, psychotherapy, and surgical treatments.[15] Based on BMI as an outcome measure, success rates were favorable with 45.8% (22/48) success among patients that received DBS who were followed for 9–50 months. In comparison, 34% (34/100) of patients in an inpatient treatment program reported by another study achieved a restoration of healthy BMI during a follow-up time of 5 years.[11] Another study on residential treatment programs reported that 39% (47/120) of participants achieved a BMI of at least 18 on discharge following a mean of 97 days in treatment.[5] Varying follow-up times may influence the rates in which a healthy BMI is achieved. In addition, amenorrhea was previously part of the diagnostic criteria for AN in female patients; therefore, studies vary in its inclusion as a criterion for treatment success.[40] As the DSM-V does not include amenorrhea as an essential characteristic of AN, we have decided to exclude it from this discussion as a factor in determining treatment success.

Neuropsychological testing was not consistently used among studies, so a direct comparison of their results was not possible. A more standardized approach to assess the diagnostic criteria of AN postoperatively should be determined in future studies. The use of clinician based tests such as the ED Examination and Yale-Brown-Cornell ED Scale may also be considered in future studies, as these are considered the "gold standard" for determining clinical diagnoses by the American Psychiatric Association.[24] A more standardized approach to comparing clinical outcomes would improve the strength of evidence for DBS as treatment for ED.

Obesity is not included in the DSM-V because of its exclusion of being a mental disorder.[1] The World Health Organization defines obesity as having a BMI of 30 or more and current clinical diagnosis relies primarily on BMI or waist circumference because of their association with type 2 diabetes, coronary heart disease, and some cancers.[33] However, recent advances in the literature suggest potential assessments of disease outcome through biomarkers from the insulin/IGF-1 axis, markers of inflammation such as C-reactive protein, and adipokines.[33] Based on BMI alone, there was 0% success rate among the five patients that received DBS for obesity with follow-up times between 14 and 39 months.[16,41,44] However, reduction in total body weight can have benefits even when BMI remains outside of the healthy range. For example, DBS patients with type 2 diabetes who lost 5–10% of their total body weight showed increased odds of reducing their HbA1c, systolic blood pressure, and triglycerides.[45] Those who lost 10–15% of body weight showed even greater improvements in these factors;[45] therefore, reductions in body weight as an outcome measure may be helpful for assessing the efficacy of DBS.

Current treatment of obesity encompasses a multimodal approach which includes pharmacotherapy, weight loss programs, and surgical treatment. Success of these treatments is limited, and many patients fail to achieve their weight loss goals. For example, a 3-year follow-up study of bariatric surgery patients found weight loss of 15.9% following gastric banding and 31.5% after gastric bypass surgery.[7] Another study found total body weight loss after 1 year ranging from 12% to 15% after use of medical devices including aspire assist, ESG, and the incisionless magnetic anastomosis system.[36] In DBS patients, weight loss varied from 0.9% to 29.5% from baseline, with an average of 13.6%.[16,41,44] In four patients followed for 30–39 months, average weight loss was 14.8%.[41,44] These results demonstrate similar rates of success in DBS compared to other surgical and procedural treatments of obesity; however, 4/5 DBS patients underwent bariatric surgery unsuccessfully before DBS for obesity, so the results following DBS may be influenced by patient selection. These patients are already refractory to bariatric treatment and this shows their motivation to lose weight by choosing to undergo further treatment in the form of brain surgery.

The typical cost of DBS surgery ranges from $33,700 to $38,600 when utilizing a standard or rechargeable implantable pulse generator, respectively.[20] This total is significantly higher than the total average cost of bariatric surgery ($14,389),[10] but is potentially similar to or lower than the total cost of intensive anorexia treatment depending on its duration, which has been reported to equal $2295 for inpatient treatment per day and $1567 for partial hospitalization.[14] Based on these comparisons, DBS for

ED when used in refractory patients may be beneficial for reducing long-term health-care cost.

Neurobiological basis behind therapeutic efficacy

The mechanisms of DBS are not fully understood, and literature generally agrees on the principle of electrical current modulating neural pathways. For example, the cortical-basal ganglia-thalamo-cortical loop is a model comprised of direct and indirect pathways all of which contribute to the initiation, inhibition, and regulation of voluntary movement.[18] This pathway contains a wide variety of ganglia, tracts, and supportive cells with their respective neurotransmitters that function to influence feedback loops for movement. The subthalamic nucleus is a common target of DBS within the basal ganglia and stimulation of it achieves immediate symptomatic relief of Parkinson's induced tremor in patients.[13,18] Immediate improvement in symptoms following DBS suggests anatomic neuromodulation while symptomatic relief in the hours to weeks may be related to stimulation provoked neural plasticity.

Choice of electrode design adds further complexity as different designs result in different stimulation fields. A monopolar electrode produces a spherical shape as the cathode is remotely located in the body while a bipolar configuration focuses the stimulation between the anode and cathode.[18] Therefore, electrode configuration must be considered when determining the best approach to maximize benefits of DBS with minimal losses or adverse effects. Directional DBS and perielectrode may help achieve more targeted stimulation as perpendicular electrical fields focus the area of stimulation more precisely over the targeted area.[39] This may clinically result in improved therapeutic efficacy and reduced stimulation "spillover" to the surrounding areas.[39]

DBS of the NAc (DBS-Nac) is the most common stimulation area in all the studies. This has shown efficacy in the treatment of other neurological syndromes, including SUD and OCD.[4,17] Furthermore, DBS treatment for ED has been summarized above to have minimal adverse effects and complications, as only 4.7% (3/64) of the total patients suffered from serious adverse effects. This is only slightly higher than the complication rate from serious adverse effects in DBS for the treatment of SUD, which is only 3.0% (1/33)[17] of the total patients. This difference may be attributed to the difference in sample sizes and/or the wide variation in stimulation areas in the ED studies as compared to the SUD studies.[17] The SUD studies all had a common stimulation parameter at the Nac. The wide variation in stimulation coordinates and parameters seen across all studies highlights the need to do further work in researching the neural pathways involved in ED. A meta-analysis comparing the efficacy of DBS treatment for ED based on location should be done once limitations of sample size and outcome measure heterogeneity have been resolved through future DBS studies on ED.

Disparity in quality in current literature

Although the overall quality of the studies in this systematic review was adequate, many studies did not establish a protocol for data collection and suffered from a lack of blind evaluation of both objective and subjective endpoints [Figure 2]. All studies were consistent in that they used DBS to treat an ED and BMI to evaluate progress. However, neuropsychiatric measures varied between the studies. While three studies used YBOCS, HAMA, and HAMD to evaluate patient symptoms,[27-29,46] the others used questionnaires and other tests. The variability in neuropsychiatric testing also limits statistical and comparative analyses. Neuropsychological testing was also performed more in studies of DBS for AN. This could be attributed to the high incidence of OCD and other psychiatric disorders in those with AN and also to the fact that obesity is not included in the DSM-V as a mental disorder.[1] However, having a standardized set of tests will make further statistical comparisons for outcome possible.[26] There were also multiple brain regions used across a small number of studies making it even more difficult to determine the efficacy of treatment. Future studies should consider determining a standard target structure to generate data with stronger analytical capabilities.

Furthermore, there was wide variability in follow-up time ranging from 6 to 50 months. Three of the studies had follow-up times of less than 1 year and most studies only had a single follow-up time point. This may influence the accuracy of reported outcomes because follow-up times under 1 year have been associated with lower reported relapse rates as compared to follow-up times greater than 1 year.[23] Furthermore, most relapses occur within the 1st year and a prior study has stressed the importance of multiple follow-ups within the 1st year.[23] Future studies should standardize the follow-up protocol and create follow-up times at 3, 6, 9, and 12 months as recommended in Khalsa *et al*.[23]

A current study hopes to explore the efficacy of DBS treatment for AN.[35] The study plans to use DBS to

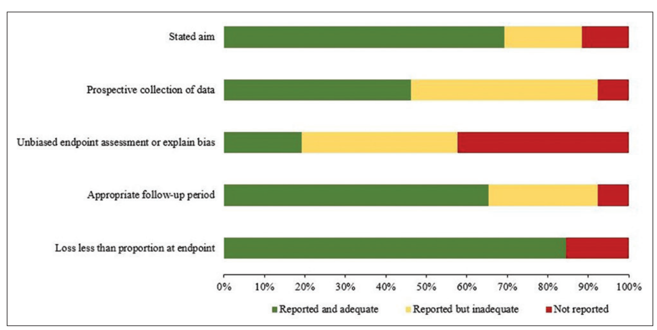

Figure 2: Percentages of publications that fulfill individual MINORS quality assessment criteria.

target the NAc in a total of six patients over a 15-month period and will assess for BMI, neuropsychological status, magnetoencephalography (MEG) to assess image neural processes, and computerized tasks to assess habit formation while also incorporating double-blinded on/off stimulation crossover phase, which has not been previously done in other studies. Comparing this study design with those of currently published studies, it is more comprehensive and accounts for prior limitations, but it is limited by its small sample size of six patients. Two of the prior studies measured glucose metabolism in the brain by PET standardized uptake[27,28,47] to visualize the active areas of the brain before, during, and after DBS treatment. While PET was used in the past, the current study opted to use MEG.[8] They aim to compare resting brain function to a food reward task to evaluate real-time neural responses to brain stimulation, which may further uncover DBSs effect on modulating activity related to food cravings.

Combining measurements of brain activity, computerized tasks, and neuropsychological status evaluation may allow for better understanding of the pathophysiology of AN and the role of the NAc. On/off stimulation was seen in a single case study and showed that the patient's symptoms worsened during "off" periods; however, this was only done during DBS treatment for obesity in a single patient.[16]

CONCLUSION

Current literature supports the use of DBS for AN and obesity through preliminary success. Although the percentage of patients achieving a healthy weight was less than half and none of the patients achieved a normal BMI in the obesity studies, the benefits of DBS in treating EDs appear to be lasting in most patients and warrant further studies. Studies should aim to increase their sample sizes, determine a follow-up protocol, and standardize the neuropsychiatric tests used to determine psychological and physiological benefits.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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