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Review

Neurostimulation Approaches in the Treatment of Severe Anorexia Nervosa

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Abstract

Psychiatry is seeking interventions that could reliably sustain weight gain and psychosomatic recovery of patients with severe anorexia nervosa (AN). Currently, patients with AN, even after receiving individually-tailored therapeutic interventions, often relapse following marginal weight restoration. Also, the evidence regarding the effectiveness of psychotropic medications in relieving and treating AN symptomology is limited. The research in the field is aiming to mitigate shortcomings associated with common practices and build on strategies including enhanced-CBT. An eminent discordance with conventional treatment modalities gives reason to explore alternative standards of care. This review explores 21st-century studies adopting neurostimulation therapies as an alternative approach for severe AN. The most widely used neurostimulation treatment in psychiatry is electroconvulsive therapy (ECT), but modern transcranial magnetic stimulation (TMS) due to its non-invasive technology has also garnered the attention of practitioners. Deep brain stimulation (DBS) is rapidly emerging as a potential (invasive) treatment. These three treatment options are further explored, and future research directions are discussed.

Keywords

Anorexia nervosa; treatment; neurostimulation; electroconvulsive therapy; transcranial magnetic stimulation; deep brain stimulation

1. Introduction

Eating disorders have a chronic and often recurring course and poor prognosis. In particular, anorexia nervosa (AN) is a relatively common and debilitating disorder with severe consequences on somatic and psychological well-being in both genders. AN is the third leading cause of chronic illness among adolescents [1-3] with the highest mortality rate among psychiatric disorders [4]. A meta-analysis investigating AN prevalence and mortality rates between 1966 and 2010 revealed the standardized mortality ratio (SMR) as 5.86 [5]. Likewise, a recent longitudinal clinical study showed the SMR for AN as 5.35 [6].

Contemporary research confirms the association of AN with psychiatric comorbidities such as anxiety disorders, obsessive-compulsive disorder, bipolar disorder, and depression. Also, AN can adversely affect many body systems due to severe weight loss and malnutrition. For example, systemic complications include cardiac abnormalities, pulmonary function abnormalities, musculoskeletal complications such as osteoporosis, structural, and functional brain impairment such as atrophy, dermatologic changes (e.g., xerosis, lanugo hair growth, acne), and hematological changes like anemia and leukopenia [7]. Given its prevalence and multifaceted list of complications, diagnosis, and recovery of patients with AN are challenging.

In persons with severe AN, a serious impediment is the indications often going unnoticed in the early stages of the disease. When AN is diagnosed, the specific clinical benchmarks helping to delineate consideration of inpatient versus outpatient care as a first-line intervention and when to discharge or end outpatient care are not always obvious [8]. The most effective treatment modalities for severe AN also remain unclear [9]. Most importantly, treatments typically focus on weight gain and psychological recovery of patients, inevitably jeopardizing compatibility between patient aims and readiness for recovery, resulting in high drop-out rates [9]. While research in the field is aiming to mitigate shortcomings associated with common practices, eminent discordance with conventional treatment modalities is the reason to explore alternative standards of care [10-13].

This review aims to provide a summary of conventional praxis for severe AN and reviews 21st-century studies adopting conceivably unconventional brain stimulation therapies as an alternative approach. Relevantly, neurostimulation is a method intended to change the nervous system function through the use of energy fields, including electricity, magnetism, or both. Contemporary neurostimulation methods use a variety of invasive (surgical implantation) and non-invasive mechanisms to augment or suppress neuronal activity for the treatment of disease. The most widely used neurostimulation treatment in psychiatry is electroconvulsive therapy (ECT), but modern transcranial magnetic stimulation (TMS) is also gaining attention due to its treatment potential and fewer side effect while remaining non-invasive. Moreover, deep brain stimulation (DBS) is emerging as a potential, although more invasive, treatment for AN. The three treatment options are further explored here.

1.1 Overview of Contemporary and Conventional Treatments

1.1.1 Psychotherapeutic and Psychosocial Interventions

A recent meta-analysis [14] examined the efficacy of psychological treatments including cognitive behavioral therapy, psychoanalytic therapy, interpersonal and family therapy, social skills training, motivational interviewing, and their combination compared to control on outcomes including weight gain, eating disorder pathology, and quality of life among adolescents and adults with AN. Across 17 randomized control trials between 1980 and 2017, with a total of 1279 participants (n = 761 in the treatment condition), the analyses did not find significant differences between the treatment and the control groups suggesting non-alleviation of the ailment by the therapeutic interventions. However, this was not the first study to report the lack of treatment effect [15, 16].

Another meta-analysis explored the efficacy of different treatments for patients with AN [17]. The results showed that specialized treatments (whether a specified therapy or the use of pharmaceuticals) revealed a significant effect over control conditions (alternative therapies or placebo conditions) on weight-based symptoms at the end-of-treatment, but did not reveal differences at follow-up post-treatment. Therefore, the improvements did not endure, indicating inconsistency and often counterproductivity of specialized treatment interventions.

More specifically, cognitive-behavioral therapy (CBT) is a well-established evidence-based treatment addressing dysfunctional beliefs and maladaptive behaviors in patients with eating disorders and mood disorders [18]. Although further investigations of its efficacy are warranted, extant research claims CBT to be the most effective treatment in achieving remission rates in nearly 50% of patients with bulimia nervosa [19-21] and shows the most rapid improvements compared to other therapies [22]. Similarly, patients with binge eating disorder who receive CBT show remission rates of about 50% to 60% [23, 24]. While evidence supports the use of CBT for bulimia nervosa and binge eating disorder, this therapy does not result in remission in a large number of patients, and high-quality CBT has not revealed similar rates of efficacy for persons with AN [9, 25]. Despite the lower remission rates, the latest “enhanced” version of CBT (i.e., CBT-E) is a promising avenue for treating some facets of AN in adolescent and adult populations [26-28]. Currently, as studies exploring CBT-E do not include rigorous randomized controlled research designs, additional empirical support is required to draw reliable conclusions [29].

Similarly, the relative efficacy of family-based treatment and individual-focused therapy for adolescents with AN has been examined. For example, Lock et al. [30] compared treatment modalities in controlled trials to evaluate the family-based treatment and adolescent-focused individual therapy in achieving full remission. The results showed no differences in full remission rates post-treatment suggesting equal efficacy of both treatments. In line with Eisler et al. [31] at follow-up, the family-based treatment was effective in preserving full remission on BMI percentile and eating-related psychopathology compared to individual-focused therapy. Still, remission rates endured for about 50% of patients, indicating inconsistency of such intervention methods and patients without improvements requiring distinct attention and alternate care plans.

Furthermore, it is also important to recognize the contributions put forth by Schmidt and colleagues in recent years [32-34]. They developed a novel maintenance and treatment model for AN combining both intra- and interpersonal aspects called the Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA). The model encompasses four factors linked to the underlying

obsessional and anxious/avoidant personality traits central to AN maintenance and provides the foundation for developing an alternative treatment, setting this treatment apart from other therapies. One of the largest RCTs of first-line psychological treatments for adult outpatients with AN [34] compared MANTRA with Specialist Supportive Clinical Management (SSCM) [35] and found both treatment modalities result in significant improvements in BMI, eating disorder symptomatology, distress levels, and clinical impairment at 6 and 12 months with no significant difference between the groups. The findings are encouraging compared to the authors' pilot RCT comparing MANTRA and SSCM [32], suggesting continuity of these treatment options and long-term outcomes ought to be included to consider their enduring effects. Remarkably, BMI outcomes from the trial [34] were compared with outcomes from a recent German trial [36], indicating that MANTRA and SSCM show similar results as CBT-E in the treatment of AN.

In general, the evidence supporting psychotherapeutic interventions in AN is progressing. The findings reveal some benefits of family-based treatment for adolescents, but a specific modality has not demonstrated superiority for adults, although new approaches such as MANTRA demonstrate merit for examining their efficacy. Also, methodological challenges limit the scope of current research. Randomized controlled trials have not sufficiently addressed the more complex treatment approaches seen in common practices such as multidisciplinary treatment and levels of care [9]. As research advances, improved psychotherapeutic methods increase treatment efficacy particularly, in combination with neurostimulation.

1.1.2 Pharmacological Treatments

A recent large-scale meta-analysis of randomized controlled trials (n = 2524) examined the effects of diverse treatment options on AN-related outcomes [17]. The findings revealed no effects when comparing psychosocial and pharmacological treatments on weight indices or psychological outcomes at the end-of-treatment and follow-up post-treatment. There are no lasting effects of distinct treatment modalities for AN symptomatology following the weight maintenance phase. Patients with AN often relapse following weight restoration even with the use of antipsychotic or antidepressant medication. Since the treatment of AN is multidimensional and often includes several targets like nutritional rehabilitation and cognitive-behavioral rejuvenation, it is difficult to understand the role of medication. Although psychotropic medications are used to alleviate mood and anxiety in patients with AN, these conditions are ineffective treatment adjuncts. To date, there is limited evidence of the efficacy of medication in relieving and treating AN, especially for acute management [37, 38].

Contrarily, some medical experts [7] advise remedy by using low-dose antipsychotics for delusional beliefs about body size, ruminations about food and diet, and anxiety-provoked experiences from having to deal with time-sensitive weight restoration. For instance, fluoxetine is a selective serotonin reuptake inhibitor antidepressant affecting unbalanced chemicals in the brain in people with depression, anxiety, panic, or obsessive-compulsive disorder. Kaye et al. [39] showed that fluoxetine assists in preventing relapse in weight-restored patients diagnosed with AN. However, the study had major limitations. Furthermore, the findings have not been replicated in subsequent randomized controlled trials [40, 41].

Some practitioners include antidepressants in the weight maintenance phase of treatment, but they do not restore eating disorder pathology in acute underweight patients [7]. The poor response

to antidepressants is due to starvation-induced abnormalities in serotonin receptors. Underweight patients do not have the nutrients required to make or absorb serotonin, thus preventing the effect of selective serotonin reuptake inhibitors [42]. Barbarich et al. [40] conducted a double-blind, placebo-controlled trial where underweight AN-diagnosed subjects received either nutritional supplements or a nutritional placebo during fluoxetine uptake. The nutritional supplements included tryptophan (i.e., the precursor of serotonin), vitamins, minerals, and essential fatty acids influencing serotonin pathway function. The results revealed no difference in weight gain between subjects treated with fluoxetine plus nutritional supplements versus fluoxetine plus the placebo. Therefore, poor response to antidepressants by patients with AN remains unclear. Another mechanism is the dysregulation of serotonin receptors [42].

The usefulness of pharmacotherapy in AN with- and without comorbidities is debatable. Fortunately, treatment advances are arising from neuroscience-based interventions probing and targeting cerebral mechanisms [43, 44]. Emerging evidence suggests the potential for alternative informed and effective treatment options to aid in achieving remission and recovery in severe and treatment-resistant cases.

2. Non-Invasive Neurostimulation Treatment Options

The efficacy of brain stimulation therapies is limited in the literature. Although invasive techniques exist, such as deep brain stimulation (DBS: a surgical procedure requiring a well-equipped medical team including neurologist and surgeon), non-invasive techniques including ECT and TMS are increasingly employed in practice and administered without difficulty by a psychiatric team for both inpatients and outpatients. This section provides a review of 21st-century research using non-invasive ECT and TMS treatment methods.

2.1 Electroconvulsive Therapy

ECT is a highly effective and judicious somatic therapy compared to psychopharmaceutical alternatives for the management and treatment of severe mental illnesses (i.e., melancholic and major depression, catatonia, bipolar disorder, and resistant schizophrenia). According to the American Psychiatric Association [45], ECT is a medical treatment most commonly used in patients with severe major depressive disorder or bipolar disorder, not responding to other treatments, including medications and psychotherapy. The process requires electrodes to be placed on the scalp of the patient under general anesthesia, and controlled electrical current is administered by qualified medical professionals. This electrical current intentionally triggers a short-lived seizure causing changes in the brain to relieve severe symptomology. Although the mechanism of the induced seizure improving neuropsychiatric symptoms is not understood, hypotheses are being explored around the neuro-physiological, neuro-biochemical, and neuro-plastic changes observed in the brain [46]. The growing evidence reveals multiple neurobiological mechanisms for the therapeutic effect of ECT [47]. Depression studies, through neuroimaging, repeatedly show the medial temporal lobe, including the hippocampus and amygdala, and the anterior cingulate cortex increasing in volume after ECT [47]. Furthermore, various neuro-physiological and neurochemical changes in the macro- and micro-environments of the brain have been documented [46]. Despite the criticisms and controversies, ECT is used in clinical practice due to its relative safety and efficacy.

The idiosyncratic parameters affecting both the effectiveness and side-effects of ECT are the frequency of treatment, dosage, and placement of electrodes. The parameters producing the most effective outcomes with the fewest side effects are debatable. A recent study showed that the efficacy of common electrode placement (bifrontal, bitemporal, and right unilateral) at three treatments weekly among patients with major depressive disorder revealed no significant group differences [48]. The results suggest the benefits of focal placements. Bai et al. [49] examined the direct effects of 10 alternative and novel ECT electrode placements relative to the three conventional electrode placements in a simulation study. Their results propose an alternative placement (frontoparietal) important for ECT efficacy while limiting memory-related side effects. However, clinical trials are necessary to confirm these findings. In general, clinicians continue to use individual-tailored treatment plans, considering all the patients' symptoms, history, and prognosis.

Although ECT is not new for the treatment of severe AN [50, 51], extant research is primarily limited to case studies since ECT is seldom considered for AN and other eating disorders [52]. Even when AN is life-threatening, ETC is often overlooked. To the best of our knowledge, there are no randomized controlled trials testing the efficacy of ECT in AN, and similar findings were reported earlier [53]. Nevertheless, some research demonstrates encouraging trends supporting ECT in severe AN and ought to be explored as a viable option.

A recent case report detailed the effects of ECT in a 16-year-old female diagnosed with AN with a BMI under 17 kg/m2 [38]. Psychometric tests revealed that she experienced no depressive symptomology or psychosis. After refusing to continue with psychotropic medications and the lack of observable improvements throughout CBT, she dropped to a BMI of 16. Bitemporal ECT was introduced as an emergency response and continued for six sessions over two weeks. Following ECT, CBT was reintroduced and continued over several weeks. The patient showed substantial improvement and gained 4 kg. The case demonstrates the effectiveness of ECT in severe AN in the absence of comorbidities.

Another case epitomizes a challenging but common presentation of two clinically impairing problems, treatment-resistant major depressive disorder and AN. A 17-year old female was referred to an eating disorder program for depression, suicidal ideation, and AN [54]. After several attempts with medication and no response to pharmacological or group therapy, and increasing severity of self-harm (abusing laxatives, self-starvation, and cutting), ECT was recommended by two child psychiatrists. She underwent a total of 31 ECT treatments (10 right unilateral, followed by 21 bilateral placements) over 13 weeks. After switching to bilateral placement, her mood elevated, and her suicidal ideation and urge to self-harm diminished. At 10-weeks follow-up post-discharge, her mood and attitude further improved, and she resumed regular activities. A similar case report of an adolescent girl with severe AN and comorbid major depressive disorder with suicidal tendency following multiple failed medication trials showed complete remission from the symptoms of AN and major depressive disorder post-bilateral ECT [52].

A more recent review examined the data of adolescent case files (between 1998 and 2017) from an Israel medical center [55]. Of 667 patients hospitalized over the period due to severe AN, 4.5% of the patients (n = 30) received ECT. This subpopulation of patients was diagnosed with co-presenting major depressive disorder and with suicidal ideation. After several failed attempts with antidepressants and antipsychotics, ECT was introduced. The results showed significant improvements in acute depressive symptoms, AN, and BMI following ECT. However, following discharge, 16 patients were re-hospitalized within a year for severe depressive symptoms. The other

half showed no evidence of depressive, suicidal, or eating disorder symptoms even at follow-up between 5 and 14 years post-hospitalization. This review highlights the notion of ECT not being an option for all non-responsive patients to psychotherapy and pharmacology.

Although ECT is considered an effective and safe treatment for adults, the information regarding its use in adolescents is limited. Puffer, Wall, Huxsahl, and Frye [56] reviewed adolescent ECT cases conducted between 1991 and 2013 in a tertiary medical center to understand possible side-effects and outcomes. Their findings revealed improvement in 77% of 51 adolescent patients who received ECT on the Clinical Global Impressions–Improvement scale at the end of acute treatment. In line with Lima et al. [57], ECT is deemed effective, safe, and tolerable for adolescents with severe, life-threatening psychiatric symptoms, and supports high remission rates with few and often benign adverse effects. ECT is recommended as an acute treatment option since no indications suggest its additional risk or complications in adolescents [56-58].

Moreover, while ECT use among adults is more common than adolescents, the literature about adults with AN treated with ECT is meager. For example, a 21-year old female experienced AN symptomology for several years [59]. At her lowest BMI (12.6 kg/m2), the diagnosis of both severe AN and major depressive disorder was made. As antidepressants were ineffective, ECT was initiated for a fast response. She had ten bifronto-temporal ECT sessions, and psychotropic medication was simultaneously continued. Although her depressive symptoms improved and BMI rose to 15.3, she continued experiencing AN symptomology. A few months later, her BMI was 12.2, and AN was severe. She requested ECT and received 12 bifronto-temporal ECT sessions improving her moods. Maintenance ECT (mECT; 1 treatment every 1–2 weeks) was implemented to treat her refractory AN. Within four months, her BMI rose to 16.4 without depression symptoms. However, when mECT ceased, her symptoms reoccurred. In this case, mECT had a stabilizing effect on the patient's mood and anorectic behavior.

Recent evidence suggests eating disorders as a concern among older women [60, 61] and men [62]. A case study documented the treatment of a 72-year old woman who was diagnosed with AN and comorbid refractory depression [63]. She had a BMI of 16.5 kg/m2, exercised heavily and avoided visitors. She was prescribed antidepressants to treat depression and AN, but drugs were either stopped due to intolerable side-effects or the lack of benefit. Given the dangers of AN in older adults and the enduring symptoms, ECT was recommended. She had nine sessions of ECT, resulting in remission of the depressive symptoms and improving her eating behaviors. At follow-up, she was eating full meals and appeared joyful. ECT was considered highly effective in treating her symptoms.

Lastly, a 24-year old male with a BMI of 16.5 kg/m2 was admitted to an outpatient unit for treatment of AN [64]. After a year of different drug therapies and a specialized outpatient eating disorder protocol (involving a multidisciplinary approach that included a psychiatrist, dietician, and internal medicine specialist), the man developed a debilitating form of obsessive-compulsive disorder, which resulted in the need for assistance in everyday living. Due to the lack of a pharmacotherapeutic response and the impact of his OCD symptoms on daily functioning, ECT was initiated. After undergoing a course of 12 bilateral ECT treatments across six weeks, OCD symptoms ceased completely, and his BMI hovered around 20.5 kg/m2 with few food restrictions. At the 1-year follow-up, his symptoms remained unchanged, and he was living a healthy life. Consequently, ECT helped relieve symptoms associated with OCD and AN.

At large, ECT may prove to be a particularly fast and effective treatment option for severe and disabling AN with or without comorbidities in adolescents, adults, and the elderly of both genders.

Future research is required to understand the relative impact of the therapy itself in AN and the implications of electrode placement and other parameters.

2.2 Transcranial Magnetic Stimulation

TMS is a non-invasive stimulation technology compared to methods such as electrode stimulation [65, 66]. It is deemed a painless procedure using a magnetic field to stimulate nerve cells in the brain to alter neural activity or excitability [67]. Unlike ECT, TMS does not cause seizures or require sedation or anesthesia. After each one-hour treatment session, the patient can return to their regular daily activities. According to the American Psychiatric Association Council on Research [68], TMS or repetitive TMS (rTMS) is primarily used to treat depression and anxiety, not responding to other forms of therapy.

Briefly, the procedure consists of applying a hand-held device to the patient's head above the prefrontal cortex encompassing a small electromagnetic coil controlled by a computer program to deliver short, controlled bursts of magnetic energy. As the magnetic fields move into the brain, they produce electrical currents directly beneath the treatment coil to the dorsolateral prefrontal cortex (DLPFC). Since this region is involved in decision-making and emotion regulation, it is a common target for neuromodulation-based interventions in psychiatric disorders [69]. Although the physiological and cerebral processes underlying the effects of TMS are unclear, recent reports indicating rTMS altering the neurotransmitter systems have been implicated in AN [70, 71].

TMS treatment demonstrates the capacity to improve anxiety, aches and pains, lack of energy, appetite changes associated with depression [67], and decreases obsession and compulsion [71]. Furthermore, TMS has demonstrated efficacy and acceptability in other psychiatric disorders, including bulimia nervosa [72] and addictions [73, 74]. Accordingly, TMS may improve dysmorphic mood and maladaptive eating, such as dietary restraint in severe AN and ought to be explored as a viable treatment option [75].

Interestingly, McClelland et al. [71] conducted a double-blind parallel-group study investigating the effects of one session of sham versus real controlled high-frequency rTMS in 49 individuals with AN. Selected settings were 20 trains of 5s with intertrain intervals of 55s, 10 Hz, and an intensity of 110% of the individual's motor threshold, providing 1000 pulses over 20 min. The findings revealed important differences between the two groups. Individuals who received real rTMS reported reduced eating disorder symptoms post-rTMS and at 24-hour follow-up relative to those who received the sham stimulation. McClelland et al. [76] also documented a TMS case series on five women with AN (ages 23, 30, 32, 41, and 53 years). All women had unsuccessful psychological, pharmacological, or other treatments (e.g., electroconvulsive therapy) prior to rTMS treatment. Validated scales and visual analog scales were used to measure changes over time. In general, the results showed an association of 20 sessions of rTMS with improved eating disorder symptoms and mood for all women at six months follow-up, and for 3 of 5 women at 12 months follow-up post-intervention. Although emotion regulation and eating behavior improved, BMI did not significantly change across the intervention period or at follow-up. Therefore, if severe AN requires an emergency strategy to augment weight, rTMS might be useful as a complementary treatment to mitigate anxiety and affective responses to enforced food intake.

Furthermore, Woodside et al. [77] reported a case series employing 20 to 30 rTMS treatments among a sample of 14 women diagnosed with post-traumatic stress disorder and an eating disorder.

A total of two patients were diagnosed with AN. Although the results showed improvement of PTSD symptoms for 57% of patients (and by > 50%), the two patients marked severely underweight (BMI of 15.7 and 14.5) showed little clinical improvement following TMS. This suggests the importance of nutritional rehabilitation before rTMS treatment.

Another recent case report reported a 25-year-old woman who was admitted and discharged repeatedly for severe AN (BMI of 11.98 kg/m2), anxiety, and depression [78]. Despite several medication trials (including sertraline, venlafaxine, escitalopram, quetiapine, and olanzapine), intense psychotherapy, and regime approaches (realimentation with food supplementation and sipping, CBT, cognitive remediation, and relaxation), her psychological status and weight remained unchanged following rTMS treatment. Compared to other case reports, she had a total of 10 treatments in two weeks, which were not long enough for substantial effects in severely underweight patients. Additional research is necessary to help inform the recommended number of TMS sessions for optimal outcomes.

In 2018, the first randomized controlled feasibility trial of multi-session rTMS treatment in people with AN was conducted in collaboration with the Eating Disorders Unit at the South London and Maudsley NHS Foundation Trust [79]. Participants were recruited based on the criteria of a severe and enduring form of AN (defined as an illness duration of > three years) with a BMI of less than 14 kg/m2, and completed at least one previous course of treatment. The trial consisted of allocating 20 sessions of real versus sham high-frequency rTMS in addition to treatment-as-usual. Outcomes were assessed at baseline (pre-randomization), post-treatment (1 week following the last TMS session), and follow-up (about three months post-treatment). The results indicated rTMS to be safe and well-tolerated. The real TMS group demonstrated significant improvement in BMI both post-treatment and at follow-up, although effects sizes were modest. The real TMS group also showed a significant increase in mood and quality of life compared to the sham group at follow-up. The results about quality of life are especially fruitful as the study brings to light the notion of focusing the treatment on effectively improving the patient's outlook as a first step and gateway before restoring weight status, when patients are exceedingly reluctant.

Overall, studies generally support the use of TMS in AN. Specifically, studies tend to report a clinical response in fixations on weight and calorie intake [79, 80] and improved mood [76, 79]. However, Knyahnytska et al. recently pointed out the use of conventional rTMS in most studies where its functional capacity is limited to the stimulation of superficial cortical regions of the brain, such as the DLPFC [81]. They suggested deep TMS (dTMS) is necessary to reach deeper areas of the brain, such as the insula. The insula is an important region in AN pathophysiology due to its presumed role in gustatory modulation and feeding behavior and in the processing of interoceptive stimuli and self-awareness. In a pilot study, they tested 42 dTMS treatment sessions on eight women with severe and enduring AN. The participants received dTMS five days weekly over the first six weeks, and then twice weekly for six more weeks. The results showed dTMS is relatively safe and well-tolerated by all patients. They also found a reduction in AN-related obsessions and compulsions, and depression and anxiety scores from baseline to the end of the trial. Since it is a novel treatment method, a randomized controlled trial comparing real versus sham dTMS in a larger sample is needed to further test the efficacy in severe AN.

Additional pre-registered trials are currently underway exploring and comparing high-frequency versus low-frequency real versus sham rTMS for bulimia nervosa and AN [82-85]. The results from impending studies will help shape the direction of future initiatives with TMS.

3. Invasive Neurostimulation Techniques Emerging in Treatment-Refractory AN

3.1 Deep Brain Stimulation

As mentioned above, DBS is an invasive form of neurostimulation at an early stage in severe AN (for a systematic review of experimental studies see [86]). In brief, DBS is a reversible, non-lesion neurosurgical procedure delivering electrical pulses to specific neural targets via electrodes connected to an implantable device in the chest. Although DBS shows potential as a treatment for eating disorders such as morbid obesity and AN, the nature of this treatment remains investigational. Oudijn et al. [87] suppose that DBS of the nucleus accumbens (NAc) and other areas, such as the anterior cingulated cortex (ACC), might be effective targets for patients with severe and treatment-refractory AN. They anticipated progressive restoration of weight and improvement in core symptoms and associated comorbidities by DBS.

Lipsman et al. [88, 89] conducted an open-label trial of subcallosal cingulate (SCC) DBS on 16 female patients (between the ages of 21 and 57) with severe and treatment-refractory AN. The findings indicated that surgery was generally well-tolerated but associated with some adverse events, including an intraoperative panic attack by one patient, a seizure during the programming (2 weeks postoperative) for another patient, and other undesirable effects including nausea, air embolus, and pain post-surgery. The authors also documented that the average BMI at surgery was 13.8 kg/m2 and at the last follow-up (12 months) was 17.3 kg/m2, revealing significant improvements. DBS was also associated with significant improvements in measures of depression (Hamilton Depression Rating Scale), anxiety (Beck Anxiety Inventory), and affective regulation (Dysfunction in Emotional Regulation Scale). For six patients, changes in cerebral glucose metabolism were also noted in the insula, an area involved in interoception and homeostasis, and in the parietal regions, which are involved in body perception.

Wu et al. [90] examined the effect of the bed nucleus of the stria terminalis (BNST) DBS on BMI in four adolescent females with severe refractory AN. According to the findings, BMI increased at three months (the first measure following baseline) for all four patients and continued to increase throughout the first year, thereby establishing normal weight BMIs within 12 months. At follow-up after 2 and 3 years, BMI remained relatively stable and the average was 19.6 kg/m2. All four patients weighed greater than 85% of expected body weight by the end of the trial and no longer met the diagnostic criteria of AN.

Moreover, Blomstedt et al. [91] studied a 56-year-old woman who consented to DBS for major depressive disorder and severe AN. After many failed attempts with psychotherapy, several different classes of antidepressants (e.g., selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, mood stabilizers, neuroleptics, ketamine infusions), and rTMS with little or no effect, the patient tried ECT. After years of maintenance-ECT, attempts to reduce the frequency resulted in several suicide attempts. Long-term ECT ultimately caused a gradual loss of memory, so the treatment was stopped, and the patient agreed to partake in an ongoing study with DBS. The case study showed marginal improvements with DBS electrodes in the medial forebrain bundle (MFB) in the posterior hypothalamic area. The blurred vision became problematic when the voltage was increased throughout the treatment. After two years of the procedure, the electrodes were removed and re-implanted in the BNST. Gradual but profound improvement was documented at 6 and 12 months with BNST DBS. Her depressive symptomology

was relieved, and her anxiety and obsessive thoughts about food were eliminated. Since BMI status did not improve, the re-introduction of behavioral training helped restore healthy eating behaviors to increase her food consumption and augmented her BMI.

Overall, the advancement of DBS has unveiled new opportunities to access and cross-examine malfunctioning brain circuits and test the therapeutic potential of regulating these circuits in a variety of disorders [92]. Although the first indications show that DBS could be used to treat some patients with AN, there is precedence for clarifying issues related to ethics and patient safety to guide new research trials in the area of eating disorders [93, 94]. For instance, the patients and their cerebral areas to be targeted ought to be clarified. Furthermore, larger efficacy studies exploring the functional effects of DBS in AN are required. In the meantime, some governing bodies like the FDA require multiple conventional treatments and ECT or TMS before considering a clinical trial with DBS for patients with severe and refractory AN [94].

4. Discussion

There is no consensus on treatment guidelines for AN [53]. Furthermore, the role of psychopharmaceuticals is not clear, except in the case of major depressive disorder [59]. Hence, there is a need for effective therapy resulting in rapid improvement, particularly for patients with severe and life-threatening AN. According to advances in etiological research, there is a demand for the development of more targeted, brain-focused treatments. ECT (and mECT), TMS (rTMS and dTMS), and DBS are rapidly emerging as novel intervention methods, particularly when traditional practices fail.

Based on the current review of 21st-century case studies, both ECT and TMS generally result in favorable outcomes when other treatments do not produce desired effects. However, the findings are not robust and ought to be interpreted with caution. There are seldom cases demonstrating no treatment effects [78]. It is also likely that additional cases where ECT or TMS did not alleviate AN symptomology are not reported or published for the broader scientific community to access. Challenges and unforeseen consequences must be documented and disseminated to provide a comprehensive understanding of treatment effects.

Similarly, DBS demonstrates promising evidence of beneficial effects in mood-related circuits leading to an increased interest in using it for alleviating AN. The procedure is used in multiple targets of the neurocircuitry of AN, such as the nucleus accumbens (NAc), SCC, subgenual cingulate, and BNST [86] to directly intervene in illness driving circuits while addressing particularly high rates of comorbid mood disorders and/or anxiety [92]. Nevertheless, understanding its efficacy, consequences, side effects, and health and safety implications are in very early stages. Thus, DBS remains an experimental approach for the treatment of AN, and additional trials are needed to sanction and recommend DBS as an alternative clinical treatment modality.

Future research should also aim to identify the parameters for neurostimulation therapies such as electrode placement, pulse width, and the number of sessions leading to optimal health and recovery outcomes. Brain stimulation treatments should be considered as complementary modalities to psychotherapy. The neurostimulation treatments can be used at an earlier stage in diagnosis before more unwanted weight loss and thus prevent further invasive treatments, such as nasogastric feeding, and decrease the patient's risk (particularly for surgical procedures).

According to the review, future research should also include boys, men, and seniors. The occurrence of AN is climbing in adolescent and adult men. Research indicates that one-third of those suffering from AN and one-fourth from bulimia nervosa are men, and nearly equivalent numbers of men and women suffer from binge eating disorders [95, 96]. Hence, the notion of eating disorders being a predominantly female-experienced domain has lifted given that recent evidence suggests that males are approaching parity in terms of the pervasiveness of body dissatisfaction and body dysmorphia. Similarly, future studies should document anorectic experiences among seniors because evidence-based treatment is surely lacking [97-99]. Since AN treatment goals include restoring weight and treating somatic complications, it is particularly important to uncover the implications of ECT and/or TMS in older persons due to their fragile health. Older persons with AN are especially vulnerable to loss of bone mass and more susceptible to fractures and osteoporosis [100], among other complications. Hence, this population may also require rapid aid in achieving remission.

Given the limited scope of research in the area, prospective research must investigate ECT and TMS in randomized controlled trials with enough power (i.e., large sample sizes) for reliable conclusions. New research is encouraged to also compare ECT and TMS in severe AN to help distinguish the advantages and disadvantages and bring to light the efficacy of such treatment modalities in terms of evaluating the side effects, effectiveness on emotional, behavioral, psychological and somatic outcomes, remission rates, and duration of remission. Currently, TMS is more accepted by the general community and perceived as safe compared to ECT. However, TMS has only been a treatment option in most Western cultures since the early 2000s and has limited evidence in AN. Likewise, ECT has limited evidence in AN even though the practice is widely used for other critical psychiatric conditions. Yet ECT maintains its reputation as a useful treatment option for clinicians and patients facing critical and emergency circumstances. Overall, the knowledge around neurocircuitry involved in AN [101] has given rise to the use of neurostimulation methods [102, 103], and further scientific support is underway to help inform new research directions and its practical application.

5. Conclusions

At large, studies on neurostimulation as treatment methods for AN have led to promising outcomes in severe cases. While evidence continues to emerge, neurostimulation methods have significant potential in advancing the science behind disease mechanisms and as an intervention [104].

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