Published in final edited form as:

Clin Ther. 2021 January ; 43(1): 85–94. doi:10.1016/j.clinthera.2020.11.006.

Current Therapeutic Approaches to Anorexia Nervosa: State of the Art

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Abstract

Anorexia nervosa (AN) is a devastating psychiatric disorder characterized by extreme restriction of food intake and low body weight, both associated with significant medical and psychological morbidity. The clinical severity of AN has prompted the consideration and study of behavioral and pharmacological treatments in efforts to establish empirically based methods to reduce the burden of the disorder. Among adolescents, family-based treatment is considered a first-line behavioral treatment. Research continues to explore the efficacy of family-based treatment and predictors of treatment response to further improve outcomes. Several behavioral treatments for adults also exist, including cognitive-behavioral therapy, exposure and response prevention, third-wave acceptance-based treatments, and supportive psychotherapy, all of which help to improve symptoms and promote modest weight gain. Despite this, no one treatment is considered superior, and all existing behavioral approaches leave a proportion of adults symptomatic or at a high risk of relapse. As such, among adults, there is continued need for development of novel, mechanism-based approaches to better target the core symptoms of AN. Although antidepressants impart little benefit on weight or symptoms, the second-generation antipsychotic olanzapine has shown ability to promote modest weight gain in outpatients with AN. Most recently, the field's evolving conceptualization of AN as a biologically based disorder coupled with technological advancements has led to consideration of varying neuromodulation strategies as a potential therapeutic approach that remains under investigation.

Keywords

anorexia nervosa; eating disorders; medication; neuromodulation; psychotherapy; treatment

INTRODUCTION

Anorexia nervosa (AN) is a devastating psychiatric disorder characterized by extreme restriction of food intake and accompanied by significantly low body weight, fear of weight

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DISCLOSURES

Dr. Attia serves as a clinical advisor to Equip Health, Inc., and receives royalties from UpToDate. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

gain, and preoccupation with body shape or weight.[1] AN is associated with myriad medical complications and psychological comorbidities, and it carries one of the highest mortality rates of any psychological disorder.[2–4] Although incidence estimates vary, AN affects both women and men across a variety of ages and backgrounds, with an estimated lifetime prevalence of ~0.8% of adults in the United States alone.[5,6]

The clinical severity of AN together with its long history[7] have led to the consideration and study of behavioral as well as pharmacological treatments for AN in efforts to identify and establish empirically based methods to reduce the burden of the disorder. Recent years have also seen an increase in investigation of neurostimulation and neuromodulation as potential therapeutic strategies. The present review describes the extant literature on therapeutic approaches for AN, with emphasis on some of the field's most recent developments. Overall, adolescents with AN respond well to treatment, with family-based therapy being consistently associated with improvements in both weight and psychological symptoms. Adults with AN have more limited response to treatment, with low rates of symptom remission and significant rates of posttreatment relapse. As such, new treatments are needed for adults with AN.

Behavioral Management and Psychotherapy

Of the different categories of treatment available, behavioral approaches are commonly used to help individuals with AN change behaviors of food restriction and associated features of illness, including excessive physical activity and other compensatory behaviors aimed at preventing weight gain. Clinicians and researchers have worked tirelessly to identify predictors of AN and establish theoretically based protocols to treat its symptoms. As a result, numerous psychological supports and behavioral interventions have been developed, including family-based, cognitive-behavioral, and related approaches, all aiming to help patients normalize weight and eating behavior. The following sections detail the range of interventions currently available and their reported efficacy.

Family-Based Treatment

Family-based treatment (FBT), also known as the Maudsley method,[8] is considered the gold standard treatment for adolescent AN. FBT was developed as an outpatient treatment that adopts an agnostic stance regarding the etiology of AN and conceptualizes family as a vital resource through which adolescents can achieve recovery. Parents are tasked with the responsibility of taking back control from AN and restoring their child to wellness, while siblings of the patient function in a supportive role. Therapists guide the family through 3 phases: (1) re-feeding and weight restoration; (2) gradually returning responsibility to the adolescent: and (3) establishing a healthy adolescent identity.[8,9]

Research evaluating the efficacy of FBT has found evidence for its short- and long-term effects. In a study of 121 adolescents with AN who received FBT versus adolescent-focused individual therapy for 12 months, FBT was associated with improvement in symptoms, with 89% of the sample reaching full or partial remission by end of treatment (EOT), and 78% reaching full or partial remission at the 12-month follow-up.[10] When directly compared

against outcomes with adolescent-focused individual therapy, both treatments had comparable remission rates at EOT, although FBT yielded significantly higher rates of full remission at the 6- and 12-month follow-up visits. FBT was also associated with higher rates of partial remission, greater body mass index (BMI) percentile, and greater changes in eating disorder symptoms at EOT, although these differences were no longer present at follow-up. Another study of 32 adolescents with AN receiving FBT found that 78% of patients no longer met criteria for AN at the 36-month follow-up.[11]

More recently, there has been focus on development of separated forms of FBT, whereby sessions are held with parents only rather than the entire family. Indeed, research indicates parental involvement may be the mechanism driving short-term change: a randomized controlled trial (RCT) comparing remission rates between FBT and parent-focused treatment in 107 adolescents found parent-focused treatment superior to FBT at EOT, with no differences at follow-up.[12] With regard to predictors of treatment response, research has found that weight gain early in treatment is predictive of better outcome in both conjoint and separated models of FBT,[13,14] and that this is facilitated by increasing therapeutic alliance and decreasing negative emotion and parental criticism.[13]

Although FBT is primarily delivered in outpatient settings, there are many adolescents for whom more intensive treatment may be appropriate. FBT may still be indicated in these cases, and for these reasons it has been adapted to higher levels of care. In a study of acceptability, the parents of 58 former inpatients with AN reported high levels of satisfaction with inpatient FBT.[15] FBT may also be an effective step-down treatment immediately after an inpatient stay: in a study of 82 adolescents with AN, shorter and longer hospitalizations yielded similar outcomes when treatments were followed by 20 sessions of outpatient FBT.[16]

Taken together, the current research on FBT indicates it is an effective intervention and supports its use as the gold standard behavioral treatment for adolescent AN.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) remains one of the widely used behavioral therapies in the treatment of eating disorders, including AN. Initially developed for depression,[17] CBT was first loosely used as a theoretical approach for understanding AN.[18] Later iterations of CBT for AN elaborated on this approach and proposed that symptoms were maintained by an overvaluation of shape and weight.[19] CBT for AN was initially found to be useful in preventing relapse after inpatient hospitalization[20] but did not show improved outcomes relative to other treatments.[21] Fairburn[22] subsequently extended the CBT model of bulimia nervosa to a transdiagnostic model of eating disorders with an enhanced form of CBT (CBT-E), designed to treat psychopathology shared across eating disorders. CBT-E is conventionally administered over 40 sessions, focusing on regularizing eating patterns, eliminating exercise or other compensatory behaviors, and challenging cognitions supporting overvaluation of shape and weight.

As a whole, CBT-E has shown feasibility and acceptability, with an average of two thirds completing treatment.[23,24] In a sample of 99 adults receiving outpatient CBT-E with no concurrent treatment, 64% completed treatment.[23] Another study of 49 adults and 46 adolescents receiving CBT-E reported completion rates of 63% and 65%, respectively.[25] Research also suggests that CBT-E is associated with improvements in weight and symptoms: the 99 adults who received CBT-E with no concurrent treatment reported a marked improvement in weight and eating disorder symptoms by EOT. Among completers, there was an average weight gain of 7.5 kg, and approximately 90% of individuals reported minimal eating disorder symptoms, despite having gained weight.[23] Moreover, the majority of these treatment gains were well maintained at the 60-week follow-up. Notably, this study examined the effects of CBT-E on patients within a BMI range of 15.0–17.5 kg/m^2 and for a limited time following treatment; additional research is needed to investigate whether these findings can be generalized to individuals with a larger range of BMIs and over longer follow-up periods.

Although initially designed as an outpatient treatment, CBT-E has also shown success in inpatient settings. In an RCT comparing 2 forms of CBT-E in 80 inpatients, patients receiving broad versus focused versions of CBT-E exhibited significant and comparable improvements in weight and symptoms, with only minimal deterioration in progress over the first 6 months of follow-up.[26] Research comparing CBT-E versus other treatments is limited, although findings suggest that its effects are comparable: in an RCT of 242 adults with AN randomized to undergo CBT-E, focal psychodynamic therapy, or optimized treatment as usual (TAU), patients receiving CBT-E exhibited equivalent weight gain and recovery rates at EOT and 12-month follow-up.[27]

In sum, CBT-E remains one of the leading treatments for AN and has been proposed as an alternative to FBT for adolescents[28] but its efficacy relative to other treatments has yet to be established.

Mechanism-Based Behavioral Treatments on the Horizon

The general success of behavioral therapy, together with an evolving interest in mechanism-based exploration of AN, have led to additional treatment strategies investigated in several studies. Habit-centered models of AN were investigated in 2 interesting pilot studies. Exposure and response prevention, known for its use in the treatment of obsessive-compulsive disorder, was adapted for AN (AN-EXRP) and compared with cognitive remediation therapy (CRT) in a randomized controlled pilot study of 32 hospitalized patients.[29] Those receiving AN-EXRP reported an average increase in caloric intake from pretreatment to posttreatment, compared with those receiving CRT, who reported decreased caloric intake. Among patients who received AN-EXRP, improvements in caloric intake were associated with decreases in meal-related anxiety. A subsequent small-scale trial of 22 hospitalized patients with AN aimed to use a behavioral intervention (i.e., Regulating Emotions and Changing Habits [REaCH]) incorporating habit reversal, including cue recognition and behavioral interruption, to disrupt eating disorder behaviors.[30] In this study, patients received 12 sessions of either REaCH or supportive psychotherapy as an active control. Compared with the control group, those in the REaCH group experienced a greater

decrease in eating disorder symptoms and self-reported habit strength, providing support for a habit-based model of AN. Additional research devoted to building on these interventions that more specifically target a habit-centered mechanism for AN is worth further exploration.

CRT is another mechanism-based treatment used to treat AN. Originally designed to improve functional outcomes in patients with neuropsychiatric disorders, CRT has since been adapted to AN based on the theory that its symptoms stem from poor central coherence and deficits in set-shifting.[31] A recent meta-analysis of RCTs examining CRT suggests it yields some improvement in both central coherence and set-shifting but is not superior to control treatments.[32] A more recent RCT of 61 adults with AN was the first to compare CRT versus an active control, specialized attention therapy.[33] This study compared 20 sessions of CRT versus 20 sessions of specialized attention therapy and found no differences in rates of treatment completion or dropout, changes in cognitive ability, or improvements in AN symptoms. These findings suggest that CRT may not confer benefit beyond that of other available treatments.

Third-Wave Treatments

The last 2 decades have witnessed the implementation of “third-generation” cognitive-behavioral interventions, including acceptance and commitment therapy (ACT)[34] and dialectical behavioral therapy (DBT).[35] These interventions emphasize the importance of acceptance and mindfulness in tolerating distress and reducing maladaptive behaviors. Given the rigidity and avoidance behaviors characteristic of AN, third-generation treatments have been considered as potential interventions. Case and pilot studies of ACT and similar acceptance-based treatments for AN report improvements in weight and eating disorder symptoms,[36–38] and that the addition of ACT to TAU may result in lower rates of rehospitalization for 6 months after discharge.[38] In an RCT of 43 adults with AN, Parling et al.[39] compared the effects of ACT with TAU after 9–12 weeks of day treatment. Although there were no differences in rates of recovery or relapse, those receiving ACT had a greater likelihood of achieving a good outcome. The empirical basis of DBT for AN is less studied, although preliminary research on DBT-based treatments for AN reports improvements in BMI and reductions in eating disorder symptoms.[40–42] Additional research, particularly RCTs, evaluating the efficacy of third-wave treatments is still needed.

Other Psychological Supports

In addition to the treatments discussed here, other psychological supports, some of which were developed as comparison treatments for RCTs, have been associated with modest clinical improvement. One such example is specialist supportive clinical management (SSCM), a therapeutic approach that combines clinical management and supportive psychotherapy. SSCM was developed as an active control treatment in a clinical trial comparing CBT and interpersonal psychotherapy for AN.[43] In these and later trials of theoretically based interventions in adolescent and adult AN, SSCM produced equivalent and, in some cases, superior outcomes in the short term,[21] lending support for its status as a behavioral treatment.[44] Another promising outpatient treatment for AN is the Maudsley

Model of Anorexia Nervosa Treatment for Adults (MANTRA), which posits that the development of AN is the result of biological, interpersonal, and cognitive factors. Treatment includes a combination of psychoeducation, collaborative goal setting, and motivational interviewing styles to enact change. Clinical trials evaluating MANTRA suggest it provides clinical benefit comparable to that of SSCM.[45,46] An RCT comparing MANTRA and SSCM in 142 outpatients with AN noted comparable improvement in BMI, eating disorder pathology, distress, and clinical impairment at the 6- and 12-month follow-up.[46] Furthermore, those receiving MANTRA rated treatment as being more acceptable at the 12-month follow-up, suggesting that MANTRA may be perceived as more favorable.[47]

Taken together, results from studies of behaviorally focused psychotherapies for AN suggest that FBT is a first-line treatment for adolescents and that for adults, a number of approaches are associated with modest improvement, especially in weight status. In adults with AN, no single treatment seems to perform better than the others, although most studies were not designed as head-to-head comparison trials. Of note, outpatient treatments for adults do not generally achieve complete weight restoration during the active treatment trial period, although it is unclear whether longer treatment duration would have a different impact on outcome. Because there is no current gold standard for adult AN, substantial interest remains in developing enhanced treatments for adult patients.

Delivering Behavioral Interventions Across Treatment Settings

Although the psychotherapies described were developed as outpatient treatments, individuals with AN are often referred for treatment in settings that offer different levels of intensity.[48] Treatments such as CBT or FBT may be offered in the context of structured treatment programs that include behavioral elements such as supervised meals and group therapy. It is worth noting that many of the behavioral change goals central to the psychotherapies used for AN, including normalizing weight and eating behavior, are common across a number of interventions and across different treatment settings. Government-supported health care insurance (e.g., Medicare) in the United States has identified 5 levels of care of varying intensity, comprising outpatient, intensive outpatient, partial hospitalization, residential, and inpatient treatment.[49] Treatment referral decisions within and outside of the United States are made based on medical and psychiatric acuity, as different levels of support and supervision are recommended for individuals with AN depending on their clinical status. Treatment programs may use elements of any of a number of evidence-based treatments for this population but generally use these interventions in manners that have not been formally studied.

Pharmacotherapy

There is an extensive history of medication trials for pharmacological treatment of AN, based on the initial observation that individuals with AN exhibit core symptoms that are believed to suggest the presence of biological disturbance. Also, a number of the symptoms frequently associated with AN (eg, depression, anxiety) are responsive to medications when present in the context of other disorders. Unfortunately, these study efforts have been met with little success, as most RCTs of antidepressant and antianxiety medications in AN found

no added benefit associated with these medications compared with placebo.[50] Challenges in identifying efficacious medications in the treatment of AN are compounded by the medical side effects of being underweight and malnourished.[51] Notably, despite the lack of empirical support for the majority of psychotropic medications, many individuals with AN receiving treatment are prescribed medication, suggesting a disconnect between research findings and clinical practice.[52,53] Here, we review existing literature on the classes of medication that have received most attention, including antidepressant and antipsychotic medications.

Antidepressant Medications

Antidepressant medications were initially considered to hold promise for AN treatment due to AN's symptom overlap with other disorders responsive to these medications, including major depressive disorder, obsessive-compulsive disorder, and anxiety disorders. However, research investigating the role of these medications in the treatment of AN has largely been disappointing. Earlier classes of antidepressants, including tricyclics and monoamine oxidase inhibitors, showed no benefit and posed some risks due to side effects; as such, they are not considered safe or tolerable for patients with AN.[49,54] Selective serotonin reuptake inhibitors, including fluoxetine, citalopram, and sertraline, have a superior safety profile and are generally well tolerated among patients with AN but have not been found to be superior to placebo in promoting weight gain or improving symptoms.[54–57]

Antipsychotic Agents

Given the near delusional quality in AN of some of the beliefs around food, weight, and body image, together with rigidity, obsessionality, and intense anxiety characteristic of AN, antipsychotic medications have also been proposed as potential therapeutic agents for AN. Initial research on first-generation antipsychotic agents found few changes in weight or behavioral symptoms of AN.[58] More recently, there has been increased interest in second-generation or atypical antipsychotic agents, including olanzapine. Some,[59,60] but not all,[61] preliminary case studies and clinical trials found that olanzapine showed improvements in weight gain. In a recent large-scale, randomized, double-blind, placebo-controlled trial, 152 adult outpatients with AN were randomized to receive 16 weeks of olanzapine or placebo.[62] Primary outcomes measured were weight gain and obsessionality, as measured by the Yale-Brown Obsessive-Compulsive Scale.[63] Importantly, the olanzapine group demonstrated both a greater rate of weight gain and higher BMI at EOT, although no significant differences in psychological symptoms were noted.[62] Given these findings in combination with its documented safety and tolerability, olanzapi olanzapine represents a promising therapeutic option for promoting modest weight gain in adults with AN.

In sum, the significant overlap between symptoms characterizing AN and other psychological disorders has encouraged the field to investigate several medications effective for other diagnoses. Although most yield little to no benefit, a recent large study of olanzapine versus placebo suggests that olanzapine may be effective in promoting weight restoration among underweight patients with AN.

Treatments on the Horizon: Neuromodulation

AN is increasingly recognized in the field of psychiatry as a biologically based disorder with distinct neural underpinnings. This evolving conceptualization coupled with technological advances in the last few decades have led to emerging interest in neuromodulation as a potential therapeutic option for AN symptoms. Varying forms of neuromodulation allow clinicians to target and probe specific brain regions or circuits. Numerous studies have investigated the role of different types of neuromodulation, including repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS), as a therapeutic approach for treatment-refractory AN.

Repetitive Transcranial Magnetic Stimulation

rTMS is a form of neuromodulation reliant on electromagnetic principles, in which a coil capable of generating an electrical current is placed near the scalp. The current can be used to suppress (via low-frequency rTMS) or excite (via high-frequency [HF] rTMS) neural activity within a targeted brain region. Recent findings from case studies and sham-controlled trials suggest that rTMS may have clinical benefit for AN. With the exception of 1 study,[64] case reports of female subjects with AN found that HF rTMS targeting the left dorsolateral prefrontal cortex (DLPFC) yielded improvement in functioning; the amount of improvement reported ranged from reduction in specific symptoms to full remission.[65–69] Researchers have also conducted RCTs to compare the effects of HF rTMS to the left DLPFC versus sham treatment.[70–72] A double-blind, parallel-group study of 49 patients found that, when controlling for baseline symptoms, those receiving real rTMS exhibited decreases in self-reported urges to restrict, feeling fat, and feeling full after 1 session of HF-rTMS, and that improvements persisted after 24 h.[70] Another sham-controlled RCT of rTMS in AN found that those who received 20 sessions of real HF-rTMS to the left DLPFC experienced greater improvements in BMI and eating disorder symptoms.[72] Between-group effect sizes were small at EOT and short-term follow-up but became more pronounced over longer term follow-up, suggesting that additional improvement may occur after treatment.[73]

Transcranial Direct Current Stimulation

tDCS is another form of noninvasive neuromodulation investigated as a potential treatment for AN. It delivers a fixed, weak current, generating subthreshold changes to targeted neurons. This current can be used to increase or decrease neuronal activity using anodal or cathodal electrodes, respectively. In the first open-label pilot study in AN, 7 patients received 10 sessions of excitatory tDCS over the left DLPFC. At posttreatment, 5 of 7 patients reported decreases in eating disorder and depression measures, although these changes were only maintained by 3 of these patients after 1 month.[74] A subsequent investigation of 23 adolescents with AN compared the effects of tDCS and TAU versus the effects of a family-based therapy and TAU on weight and measures of psychopathology.[75] Improvements in psychological measures were noted in both groups, although the tDCS group reported greater increases in BMI over time and at 1-month follow-up, providing additional support for the potential utility of tDCS in the treatment of AN.

Deep Brain Stimulation

DBS is a reversible procedure by which electrodes are surgically implanted and deliver electrical pulses to target brain regions.[76] Initial case studies of DBS in patients with concomitant AN and depression found improvements in weight and eating disorder pathology.[77,78] A clinical study of 4 adolescents with severe AN reported an average of 65% increase in body weight after DBS to the nucleus accumbens.[79] Subsequent open-label trials of DBS implantation in the subcallosal cingulate and nucleus accumbens reported improvements in certain eating disorder symptoms and weight across follow-up.[80,81] Although reports of case and clinical studies of DBS suggest it has a good safety profile and is generally well tolerated by patients, the use of DBS for AN remains controversial.[82] Therefore, although initial data suggest that DBS may afford some clinical improvement, substantial research is needed to evaluate its relative risks and benefits.

Neuromodulation presents an exciting new frontier in the landscape of AN research and may allow for the development of innovative, biologically based treatments. These approaches are currently being researched as therapies for chronic, treatment-refractory individuals and are not considered first-line treatments. Although there is no current clinical indication for neuromodulation for AN, implementation of these methods in clinical trials is likely to increase substantially over the next decade as the field's understanding of the neurobiological underpinnings of AN evolves.

CONCLUSIONS

AN is a serious psychiatric illness that is challenging to treat, and early identification and treatment are crucial for better prognosis. Among adolescents, a family-based outpatient psychotherapy is associated with high rates of remission and recovery. In adults, a range of behaviorally focused psychotherapies are useful at helping these subjects with AN make modest improvements in weight. Despite this, adults who have generally been ill for longer durations are less responsive to treatment interventions, and relapse rates after acute weight improvements remain high. Although trials of antidepressant agents have been unsuccessful, the atypical antipsychotic medication olanzapine is associated with modest weight improvement. Neuromodulation treatments hold promise for helping patients with AN achieve behavioral change. Additional studies in this population are crucial, especially if they might target mechanisms underlying AN or identify core treatment components that help individuals make optimal improvements.

ACKNOWLEDGMENTS

Drs. Muratore and Attia both contributed to the research review, conceptualization, and writing of the manuscript.

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