HHS Public Access

Author manuscript

Curr Psychiatry Rep. Author manuscript; available in PMC 2023 July 01.

Published in final edited form as:

Curr Psychiatry Rep. 2022 July ; 24(7): 345–351. doi:10.1007/s11920-022-01340-5.

Psychopharmacologic Management of Eating Disorders

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Abstract

Purpose of Review—Identifying medications that may be used as therapeutic agents for eating disorders is a longstanding focus of research, with varying degrees of success. The present review consolidates the most recent findings on pharmacological treatment of three eating disorders, including anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED).

Recent Findings—Recent research suggests that olanzapine demonstrates positive effects on weight gain among outpatients with AN. There are fewer recent advances in psychopharmacological treatment for BN and BED, likely due to the relative success of prior medication trials.

Summary—Olanzapine is the first medication to safely promote weight gain among individuals with AN. Fluoxetine is FDA-approved for BN treatment, and lisdexamfetamine is FDA-approved for BED treatment. BN and BED also generally respond well to SSRIs prescribed off-label. Research on psychopharmacological treatments for other eating disorders, such as avoidant-restrictive food intake disorder and other specified feeding and eating disorders, are sorely needed.

Keywords

Psychopharmacology; Eating disorders; Medication; Anorexia nervosa; Bulimia nervosa; Binge eating disorder

Introduction

Eating disorders are a class of serious psychiatric disorders that give rise to a host of medical and psychiatric complications and confer enormous psychological, societal, and economic

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

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Conflict of Interest Dr. Attia serves as a clinical advisor to Equip Health, Inc., and receives royalties from UpToDate. The authors have no other competing interests to declare that are relevant to the content of this article.

costs [1–4]. Behavioral treatments for eating disorders typically begin with nutritional rehabilitation and normalization of eating patterns [5–8], though cases of treatment non-response and relapse persist [9–12]. Thus, identifying potential benefit associated with pharmacological agents, for use as primary or adjunctive treatments to behavioral therapies, is of great interest. The body of research dedicated to examining the short- and long-term effects of medication on the various features associated with eating disorders has several surprises, with medications demonstrating benefits from subsets of the eating disorders despite symptom overlap across diagnostic categories. Specifically, many medications are effective at reducing symptoms in bulimia nervosa and binge eating disorder without similar benefit in anorexia nervosa [13]. Additionally, medications are frequently prescribed as adjuncts to behavioral treatment of eating disorders at varying levels of care [13–17], even when some of this use is not supported by the evidence base. The present review consolidates the field's current understanding of the role of psychotropic medications in the management of the three primary eating disorders: anorexia nervosa, bulimia nervosa, and binge eating disorder.

Anorexia Nervosa

Anorexia nervosa (AN) is a debilitating eating disorder characterized by extreme restriction of caloric intake, fear of weight gain, and significantly low body weight [1]. AN is associated with myriad medical and psychiatric features [18] and has the highest mortality rate of all eating disorders [19, 20]. The primary goals of treatment for individuals with AN include weight restoration and nutritional rehabilitation [21–23], most often achieved using a medically supervised refeeding regimen [24]. However, AN is often accompanied by symptoms seen in other psychiatric disorders, including disruptions in mood, anxiety, and cognition [25–28]. The severity of AN has led to the consideration and study of pharmacological treatments, including those that help mood and anxiety symptoms in other clinical populations, in efforts to improve outcomes [29].

Antidepressants

Antidepressant medications first received consideration as a potential therapeutic strategy for AN because of their utility in treating other psychiatric disorders with overlapping symptoms, such as major depressive disorder. Across decades of randomized controlled trials (RCTs), these efforts have been largely unsuccessful at identifying benefit associated with antidepressants in AN. First-generation antidepressants such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) were used in the earliest medication trials, but due to low safety profiles and lack of therapeutic benefit, these are not recommended for patients with AN [6, 30–32]. Second-generation antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), have stronger safety profiles and are well-tolerated by patients. However, most research on SSRIs suggests that their effects on eating and weight outcomes, as well as on mood and anxiety symptoms, do not out-perform placebo [33–35]. Notably, the antidepressant bupropion is contraindicated with AN and other eating disorders due to increased risk for seizure [32, 36].

Antipsychotics

Atypical antipsychotic medications have also been investigated as potential treatments, particularly as a means to reduce cognitive and behavioral rigidity and obsessionality often characteristic of AN [37, 38••]. Research on the effects of first-generation antipsychotic medications among patients with AN report few improvements in symptoms or weight [39, 40]. Subsequent research on the effects of second-generation antipsychotics led to several studies that support a modest effect of olanzapine on weight restoration in AN [41–43]. In a recent randomized, double-blind, parallel-designed, placebo-controlled trial, 152 adult outpatients with AN received olanzapine (average dose = 7.77 mg/day, range = 2.5–10 mg/day) or placebo for 16 weeks. Primary outcomes included rate of weight gain and obsessionality, as measured by the Yale-Brown Obsessive–Compulsive Scale (YBOCS; 44]. Secondary outcomes included additional psychological measures, such as eating disorder symptoms, self-reported anxiety, and eating disorder-related impairment. Compared to placebo, olanzapine was associated with statistically significant increase in BMI over time (0.259 [SD = 0.051]) consistent with greater rate of weight gained, with individuals who received olanzapine demonstrating an average gain of approximately 1 lb more per month than the group receiving placebo. No significant improvements were noted using YBOCS or other psychological assessments [38••].

Anti–anxiety Medications

Individuals with AN regularly endorse anxiety symptoms, and pre-meal anxiety has been associated with decreased food intake in AN [45–47]. One small study used a randomized controlled, cross-over design to examine in 17 participants with AN the effects of a single dose of the benzodiazepine alprazolam 0.75 mg vs. placebo on anxiety and caloric intake in a laboratory meal. Surprisingly, neither anxiety symptoms nor caloric intake changed in association with alprazolam [48].

Psychedelics

More recently, psychedelic medications have received increased interest as potential therapeutic agents for AN. Preliminary qualitative research on the effects of ayahuasca, a serotonergic psychedelic, suggested that individuals with AN who received this medication reported a reduction in eating disorder symptoms [49]. Psilocybin, another psychedelic, has beneficial effects for individuals with other psychiatric diagnoses, such as depression and anxiety; ongoing research is now examining whether positive effects are also seen among individuals with AN [50•].

Summary of Pharmacological Interventions for AN

In sum, efforts to develop pharmacological treatments for AN thus far have been largely disappointing: antidepressant and anti-anxiety medications fail to result in significant improvements in eating, weight, or psychological outcomes compared with placebo. Antipsychotic medication olanzapine is the only medication to demonstrate efficacy in promoting weight gain among individuals with AN, though it does not appear to yield significant effects on psychological symptoms. While most psychiatric medications are well tolerated in AN, low weight and metabolic disturbances require caution when prescribing,

especially if there are cardiovascular abnormalities (e.g., hypotension, QTc prolongation) that may become exacerbated with a new medication. Again, bupropion is contraindicated in AN due to seizure risk. At present, there are no Food and Drug Administration (FDA)-approved medications indicated for AN. The poor response to medication in AN may speak to the neuropsychiatric and physiological differences in a semi-starved AN population and suggests a pressing need for additional treatment research. Patients with AN often have concerns regarding effects of medications on weight and metabolism, creating barriers to treatment adherence with medications with some efficacy such as olanzapine. Psychoeducation and attention to treatment engagement are particularly necessary for this clinical population. Importantly, despite the wealth of literature suggesting limited efficacy of medications, a substantial proportion of patients with AN are currently prescribed medications, reflecting the discrepancy between research and practice.

Bulimia Nervosa

Bulimia nervosa (BN) is characterized by a cycle of restriction of food intake, binge eating episodes, and compensatory behaviors such as self-induced vomiting, exercise, or laxative or diuretic misuse [1]. Unlike individuals with AN, individuals with BN are not at a significantly low weight. Medical complications associated with BN primarily result from purging behaviors and include electrolyte disturbances, hypokalemia, dysphagia, and parotid gland enlargement [51, 52]. The primary treatment goal for individuals with BN is the cessation of binge eating and purging, typically achieved through eliminating restriction and implementing strategies to reduce binge eating and compensatory behaviors [53]. Studies of pharmacological agents for BN have been more successful than those in AN, with several classes of medications being identified as superior to placebo at reducing BN symptoms [54, 55].

Antidepressants

There have been several successful trials of antidepressant medications in BN samples.

Early placebo-controlled trials of antidepressants demonstrated statistically and clinically significant improvement in BN symptoms associated with a variety of anti-depressant medications. First-generation antidepressants, including TCAs and MAOIs, were successful in reducing the frequency of binge eating and purging behaviors [56]. However, the adverse effects associated with certain antidepressant medications, including risk of prolonged QTc interval in patients with BN, offset the benefits [57]. As with AN, bupropion is contraindicated in individuals with BN due to increase seizure risk [57]. SSRIs are generally preferred due to their superior safety profile and utility in reducing symptoms of BN. While various SSRIs have demonstrated utility, research suggests high-dose fluoxetine is the SSRI with the greatest efficacy. An early 8-week, double-blind trial compared the effect of two doses of fluoxetine [20 mg/day vs. 60 mg/day) to placebo in 387 female outpatients with BN. Results indicated that the 60 mg/day dose resulted in reduced binge eating and vomiting frequency and that these effects were superior to both the 20 mg/day dose and placebo [58]. A subsequent trial of fluoxetine 60 mg/day in 225 male and female outpatients with BN found similar effects over 16 weeks [59]. In addition to improving treatment

response, fluoxetine also improves outcomes, whereby continued treatment of fluoxetine among individuals with BN who responded to acute treatment was significantly less likely to relapse than those who received placebo [60]. Subsequent research found similar effects of fluoxetine 60 mg/day in adolescents with BN, with substantial reductions in binge and purge frequency [61]. This body of research established both the efficacy and safety of fluoxetine and contributed to its FDA approval for the treatment of BN [62••].

Anticonvulsants

Initially developed for treatment of epilepsy, the anticonvulsant topiramate was observed to reduce appetite and weight [63] leading to an interest in its potential for reducing binge eating in BN. Two 10-week double-blind RCTs among patients with BN found that topiramate (median dose = 100 mg/day; range = 25–400 mg/day) was superior to placebo in reducing BN symptoms, body weight, and associated psychiatric symptoms such as anxiety [64–66]. While topiramate is generally well-tolerated at low doses needed for its effects on binge eating and purging behaviors, it can be associated with cognitive "fuzziness," as well as with paresthesia sensations in fingers and toes that make it uncomfortable for some users. Also, its potential weight-reducing effect should be taken into careful consideration when determining whether these medications should be prescribed off-label for an individual with BN.

Summary of Pharmacological Interventions for BN

Research on the pharmacological treatment of BN has been substantially more successful than that of AN. Multiple medications confer benefit, though fluoxetine's efficacy and tolerability together with its being the only FDA-approved treatment for BN contribute to its being a first-line medication when medication is being considered for BN treatment. Bupropion is contraindicated for individuals with BN due to the increased risk for seizure associated with its use.

Binge Eating Disorder

Binge eating disorder (BED) is the most common eating disorder diagnosis [67] and is characterized by a cycle of recurrent binge eating episodes without regular use of compensatory behaviors [1]. BED is associated with greater risk for being overweight or obese and is accompanied by medical complications associated with larger body size, including diabetes, cardiovascular risk, and nonalcoholic fatty liver disease [67, 68]. While many of these side effects are associated with obesity, BED confers even greater risk of medical complications than that seen in those who are obese without BED [69]. The primary goal of treatment for individuals with BED is the cessation of binge eating behaviors. A secondary goal of treatment may be weight loss, though providers vary in the emphasis they place on this outcome [70]. Pharmacotherapy is considered in cases where non-pharmacological treatments are not available or sufficient to achieve the treatment goals.

Antidepressants

Antidepressants are another class of medications that have been considered and often prescribed off-label for treatment of BED. Research on antidepressants for BED mirrors

that of BN, particularly given the antidepressant effects on binge eating [71]. Treatment research for BED initially focused on TCAs and MAOIs, with later consideration of SSRIs due to their superior safety profile. Research has examined the effects of numerous SSRIs, including fluoxetine, citalopram, escitalopram, and fluvoxamine. Results of most studies are promising: overall, compared to placebo, SSRIs yield a significant reduction in binge eating, with greater rates of binge eating abstinence [29]. Indeed, a recent meta-analysis of 7 placebo-controlled RCTs found that individuals receiving antidepressants had significantly higher rates of remission than those receiving placebo [72]. Despite the generally positive effect on binge eating behavior, antidepressants confer no significant change in weight among individuals with BED. Minimal effects on weight loss prompted consideration of other medication classes, particularly those known to suppress appetite and reduce weight.

Anticonvulsants

Anticonvulsants such as zonisamide and topiramate have also been examined as potential treatments for individuals with BED and obesity. Trials of zonisamide suggest this medication can reduce binge eating and weight in the short term [73, 74] and at 1-year follow-up [75], but may not be well-tolerated [71, 73]. Multiple medication trials provide support for topiramate's beneficial effects in reducing binge frequency and promoting weight loss. An initial 14-week placebo-controlled trial found that topiramate (median dose = 212 mg/day, range = 50–600 mg/day) was well-tolerated and led to reduction in both body weight (mean weight loss = 5.9 kg) and binge eating [76], improvements that were maintained after 42-week follow-up [77]. A subsequent multicenter 16-week trial (median dose = 300 mg/day, range = 25–400 mg/day) provided further support of topiramate's efficacy in improving binge eating and reducing obesity [78]. Current recommendations state that off-label topiramate prescriptions for BN should begin at 12.5 or 25 mg/day and titrate slowly to between 75 and 200 mg/day to minimize side effects [79].

Stimulants

Because of their weight suppressant effects, stimulant medications have been investigated as therapeutic agents for individuals with BED. An 11-week, double-blind RCT examined the effects of three doses of lisdexamfetamine (30 mg/day, 50 mg/day, 70 mg/day) and placebo on binge eating frequency. Results indicated that 50 mg and 70 mg doses were superior to placebo in reducing binge eating [80]. Two follow-up 12-week RCTs confirmed the superiority of 50 and 70 mg doses to placebo in improving binge eating and secondary outcome measures, including obsessive–compulsive symptoms, body weight, and global improvement [81]. The promising effects of lisdexamfetamine prompted the FDA's approval for use in BED in 2015. Subsequent studies of lisdexamfetamine provided further support for the medication's safety and efficacy and provided additional evidence that continued use may be better than placebo in preventing relapse [82]. While it is considered safe and effective, lisdexamfetamine's side effect profile and risk for misuse may make it inappropriate for certain patients [62••]. Minimal research has been done examining the effects of other stimulants on BED symptoms; a small randomized placebo-controlled study of atomoxetine suggested that compared to placebo, this stimulant medication also decreased binge eating episodes and reduced weight [83].

Summary of Pharmacological Interventions for BED

Treatment development research suggests that numerous pharmacological interventions may confer benefit on BED symptoms. While lisdexamfetamine is the only currently FDA-approved medication for BED, certain antidepressants and anticonvulsants are also generally well-tolerated and can demonstrate modest effects on binge eating. Lisdexamfetamine should be considered for individuals with BED, with careful attention paid to vital signs and cardiovascular health as these health measures may change in a high-risk patient taking a stimulant. SSRIs considered for off-label use in BED will likely offer benefit without these risks. SSRIs may also be particularly useful for individuals with co-occurring mood or anxiety symptoms in addition to BED.

Conclusion

Psychopharmacological treatment of eating disorders continues to be an area of great interest and study: myriad medications have been considered therapeutic agents, with some demonstrating more success than others. AN continues to be one of the most challenging eating disorders to treat; despite numerous trials examining the effects of several medications, olanzapine is the only pharmacological treatment that appears to confer benefit. This medication should therefore be considered a potential augmentation to behavioral treatment, particularly for patients struggling to restore weight. Pharmacological research for treatment of BN and BED has witnessed considerably greater success, as several medications appear to be helpful in minimizing symptoms. However, fluoxetine 60 mg/day and lisdexamfetamine are currently the only FDA-approved for the treatment of BN and BED, respectively. While pharmacological management of AN, BN, and BED has been extensively studied, there is little-to-no information about the use of medication in the treatment of additional eating disorder diagnoses, such as avoidant-restrictive food intake disorder and the other specified feeding and eating disorders, such as atypical AN or purging disorder. Given the challenges in treating these disorders and preventing relapse, this is an area greatly in need of further study.

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is most commonly associated with headache, dry mouth, and insomnia. Lisdexamfetamine has a greater potential for abuse and long-term treatment can result in increases in heart rate and blood pressure. Despite the medications' efficacy and safety, a subset of individuals do not respond to this treatment, suggesting need for additional behavioral and pharmacological treatments.

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