Pharmacotherapy of eating disorders

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Purpose of review
Medications are commonly prescribed in the treatment of eating disorders. In this review, we discuss relevant medications used for the treatment of bulimia nervosa, binge eating disorder (BED), and anorexia nervosa. We focus on recent research developments, where applicable, in addition to discussing important findings from older studies to provide a complete synopsis of the current evidence base for eating disorder treatment using pharmacologic agents.

Recent findings
Medications are generally useful for patients with bulimia nervosa and BED. For bulimia nervosa, antidepressant medications are the primary pharmacologic treatment and limited new research has been completed. For BED, lisdexamfetamine is reported to be generally well tolerated and effective, and is the first medication to be indicated by the US Food and Drug Administration for treatment of BED. For anorexia nervosa, there is limited evidence supporting benefits of medications. Second-generation antipsychotics, particularly olanzapine, appear to demonstrate some benefit for weight gain in anorexia nervosa, although are not advised as a stand-alone treatment. Transdermal administration of hormonal agents is also being explored for improving bone health in anorexia nervosa.

Summary
Although pharmacotherapy has established utility in bulimia nervosa and BED, further research on medications for the treatment of eating disorders, particularly anorexia nervosa, is necessary.

Keywords
anorexia nervosa, binge eating disorder, bulimia nervosa, pharmacotherapy, review

INTRODUCTION
Although medications are often not the primary mode of treatment for eating disorders, they are commonly prescribed as a supplement to other therapeutic interventions. Given the overlap in symptoms between eating disorders and other psychiatric conditions, investigators have long been interested in the possible efficacy of various psychotropic medications for individuals with eating disorders. Medications have been found to be most helpful in the treatments for bulimia nervosa and binge eating disorder (BED), whereas they have been disappointing in anorexia nervosa. This review discusses medication management for eating disorders, and will focus on the limited advances over the past 18 months where possible. To identify recent developments, we searched PubMed for relevant publications after December 2015, including placebo-controlled trials, meta-analyses, and case reports.

BULIMIA NERVOSA
The utility of medications in the treatment of bulimia nervosa has been well established. There have been many medication trials in this population that have consistently yielded clinically significant results, particularly with antidepressant medications such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs).

Antidepressant medications
Fluoxetine is the most commonly prescribed medication for the treatment of bulimia nervosa, and is the only medication with US Food and Drug Administration (FDA) approval for bulimia nervosa treatment. The largest study ($N=387$) of fluoxetine...
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KEY POINTS

- Recent developments in pharmacotherapy for eating disorders have been limited.
- Antidepressants are recommended as the primary medication option for treatment of bulimia nervosa.
- LDX which is the first medication to receive US FDA indication for the treatment of BED, reduces binge-eating frequency and weight; long-term use of LDX mirrors its safety profile in other clinical populations.
- Olanzapine has recently been reported to result in a modest increase in BMI in outpatients with anorexia nervosa, and is recommended for use in combination with other therapeutic methods.

was an 8 week, 13-site randomized controlled trial (RCT) comparing the efficacy of fluoxetine 60 mg/day, 20 mg/day, and placebo [1]. Levine et al. found that 60 mg/day was superior to placebo and 20 mg/day in reducing binge-purge frequency [1]. Specifically, patients receiving 60 mg/day reported a 67% reduction in binge eating episodes/week (45% by 20 mg/day group, 33% by placebo group) and a 56% reduction in vomiting episodes/week (29% by 20 mg/day group, 5% by placebo group). Based on these results, antidepressants are typically prescribed at higher doses when treating bulimia nervosa than when treating depression. Additionally, the presence of depressive symptoms at baseline did not predict clinical outcomes; in other words, antidepressants were found to be effective in reducing binge–purge episodes, even in the absence of comorbid depression. Fluoxetine has also demonstrated benefit over placebo in treating patients with bulimia nervosa who have responded poorly to psychotherapy [2], suggesting that medication strategies may hold promise for individuals with bulimia nervosa in instances when other therapeutic approaches are ineffective or unavailable.

In addition to fluoxetine, many other antidepressants have been useful in the treatment of bulimia nervosa, including other SSRIs (e.g., sertraline [3,4], fluvoxamine [5,6], and citalopram [7]), TCAs (e.g., imipramine [8], desipramine [9], and amitriptyline [10]) and monoamine oxidase inhibitors (phenelzine [11]). SSRIs are often considered first-line agents because of the established FDA indication and because of their favorable side-effect profile, including generally weight-neutral effects, whereas TCAs are used less frequently in part because of common adverse effects, including sedation, constipation, and weight gain.

Antidepressants are found to be similarly useful and well tolerated for the treatment of adolescents with bulimia nervosa [12]. However, increased risk of suicidality has been associated with SSRIs in younger populations [13], so it is imperative that clinicians monitor patients closely and discuss these risks with patients and families.

Antiepileptic medications

Topiramate, a medication used to treat epilepsy that is associated with effects on appetite and weight, has also been examined for utility in bulimia nervosa. In a 10-week trial of 64 outpatients with bulimia nervosa, topiramate (median dose 100 mg/day) compared with placebo was associated with significant reductions in binge eating and purging [14], as well as improvement in psychological measures [15]. However, some patients with bulimia nervosa taking topiramate have been reported to experience significant weight loss [14], which may complicate treatment for individuals for whom weight loss would be contraindicated.

Recent developments in medications for treatment of bulimia nervosa have been minimal. This may be because of the established success of current pharmacotherapy options.

BINGE EATING DISORDER

Pharmacotherapy has also been useful for BED. Notably, medications that help reduce binge eating frequency do not consistently reduce weight. Additionally, rates of response to placebo by patients with BED are high relative to those reported in medication trials for other clinical populations (e.g., obesity), suggesting that nonspecific treatment factors may contribute to short-term reductions in binge eating frequency. As many patients with BED present for assistance with weight management, medications associated with weight reduction are also relevant to this population.

Antidepressant medications

Similar to their effects in bulimia nervosa, antidepressants have generally been shown to reduce binge eating in BED. A variety of SSRIs (e.g., fluoxetine [16], citalopram [17], sertraline [18], and fluvoxamine [19]) and serotonin–norepinephrine reuptake inhibitors (e.g., duloxetine for individuals with comorbid depression [20]) have had comparable results and are well tolerated. However, most antidepressants appear to have little to no impact on weight loss in these patients.

Weight management medications

Orlistat is a lipase inhibitor that is used with reduced-calorie diets to treat obesity. Among 89
patients with BED who received orlistat vs. placebo over 24 weeks, Golay et al. [21] reported that orlistat was superior to placebo in achieving increased weight loss (−7.4 vs. −2.3%) and reduced Eating Disorder Inventory-2 scores. However, orlistat has consistently been ineffective in reducing binge-eating frequency [21,22].

Topiramate was first considered for use in BED because of its observed effect of weight loss in other clinical populations [23,24]. In a 16-week trial in 394 outpatients with BED, McElroy et al. [25] found topiramate (median dose 300 mg/day) to be superior to placebo in reducing binge eating frequency (−5.0 episodes/week vs. −3.4 for placebo) and weight (−4.5 vs. +0.2 kg for placebo). Additionally, a smaller (N = 35) 42-week open-label extension trial following a 14-week RCT reported that longer term use of topiramate resulted in sustained reductions in binge eating and weight [26]. These data were limited, however, by high attrition rates partly because of adverse effects associated with the medication, including paresthesias, dry mouth, nausea, and headache.

Guervadjikova et al. have recently examined the use of phentermine/topiramate extended release for the treatment of BED [27]. This medication combination is used in obese populations for short-term weight management. A 2015 report cited two cases in which this medication was used in obese adult women with BED for 3 months, resulting in cessation of binge eating and significant weight loss [27]. Although no adverse events were reported in either case, use of any medication with phentermine, which is a psychostimulant, should be cautiously monitored because of possible cardiovascular effects. A crossover trial to assess the efficacy and safety of phentermine/topiramate for treatment of BED and bulimia nervosa is ongoing (NCT02553824).

Stimulant medications

Owing to the appetite-suppressing effects of stimulant medications, research has recently focused on this class of medications to reduce binge eating among individuals with BED. In 2015, lisdexamfetamine (LDX) became the first medication to receive indication from the US FDA for treatment of BED. McElroy et al. [28] completed a 30-site RCT of 255 adults with BED to compare the efficacy of LDX 70 mg/day, 50 mg/day, 30 mg/day, and placebo. Treatment with 70 mg/day and 50 mg/day resulted in significant reductions in binge eating frequency, as well as greater percentages of patients achieving 4-week binge eating cessation (50% for 70 mg/day, 42% for 50 mg/day, 21% for placebo). Treatment with 30 mg/day was comparable to placebo. LDX treatment also resulted in significant improvements of Clinical Global Impression scores. Three recent RCTs have replicated these findings [29,30]. Although LDX is not indicated for weight loss, it is also associated with decreased weight, BMI, and triglyceride levels in patients with BED.

A large (N = 604) 52-week, open-label extension trial following three of the aforementioned RCTs was recently completed to assess long-term safety of 50 mg/day and 70 mg/day LDX [31]. Gasior et al. reported that 84.5% of participants experienced adverse events, although the majority were mild or moderate (e.g., dry mouth, headache, insomnia, upper respiratory tract infection), and only 9% resulted in treatment discontinuation [31]. LDX was also associated with statistically but not clinically significant increases in blood pressure and pulse. Authors concluded that the safety and tolerability of LDX was consistent with reports of its use in other populations (e.g., Attention-Deficit/Hyperactivity Disorder). Although these initial studies demonstrated few instances of serious adverse events in BED patients taking LDX, this medication has only been recently introduced for this clinical indication and physicians are advised to closely monitor patient heart rate, blood pressure, and other signs of cardiovascular health with any long-term use.

Chromium

Chromium is an essential mineral that has recently been examined for utility in BED. In a 6-month pilot study of 24 patients randomized to moderate (600 μg/day) chromium, high (1000 μg/day) chromium, or placebo, no benefit was associated with chromium for improving binge eating frequency, weight, or mood symptoms [32]. The moderate-dose group demonstrated improved glycemic control, whereas the placebo and high-dose groups did not [33]. Owing to its size, conclusions from this study are limited.

ANOREXIA NERVOSA

Many medications have been considered for the treatment of anorexia nervosa with generally disappointing results. Hence, pharmacotherapy is not typically the primary means of treatment for anorexia nervosa. However, many individuals with anorexia nervosa receive medications as part of their treatment plan, especially those who do not otherwise respond to psychotherapy or nutritional rehabilitation. The lack of response to medications may result from the complicated physiological state of undernutrition among this clinical population. Current research is continuing to seek medications that
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may benefit individuals with anorexia nervosa in weight restoration, as well as for relapse prevention.

Antidepressant medications

Symptoms characteristic of anorexia nervosa significantly overlap with those associated with other psychiatric disorders, including major depression, generalized anxiety, and obsessive-compulsive disorder. For this reason, antidepressants were initially thought of as a promising therapeutic option for anorexia nervosa. However, these medications have consistently been no better than placebo at achieving changes to weight or any associated psychological symptoms. For example, in contrast to its success in treating bulimia nervosa, fluoxetine has not been found to significantly enhance weight gain in inpatients [34] or prolong weight maintenance among recently weight-restored outpatients with anorexia nervosa [35]. Perhaps surprisingly, fluoxetine also was not shown to significantly alter measures of psychopathology in patients with anorexia nervosa. Other antidepressant trials mirror these results [36].

Antipsychotic medications

Owing to the rigidly held cognitions and high degrees of intense anxiety that are characteristic of patients with anorexia nervosa, antipsychotic medications have long been considered for treatment. Early studies on first-generation antipsychotic medications did not demonstrate significant clinical benefits [37]. However, the development of second-generation antipsychotics (SGAs) has shown more promise. Of these, olanzapine is most notable. Two small placebo-controlled trials of olanzapine – one 10-week trial among 34 day-hospital patients [38] and one 8-week trial among 23 outpatients [39] – reported modest improvements in rate of weight gain and end-of-treatment BMI associated with active medication. Among the day hospital patients, there was also a significantly greater improvement in obsessionality scores for patients receiving olanzapine. Attia et al. recently completed a large, multisite RCT in 152 outpatients with anorexia nervosa (Attia EA, Eating Disorders Research Society Annual Conference 2016). Study treatment included 10 mg/day of olanzapine vs. placebo for 16 weeks, prescribed according to a fixed, flexible-dose protocol; weekly sessions with a psychiatrist focused on treatment adherence. Although final study results have not yet been published, the preliminary analyses suggest that olanzapine was associated with a small but significant difference in rate of weight gain (E.A., Eating Disorders Research Society Annual Conference 2016). Olanzapine was generally well tolerated, with the most frequent side-effect being drowsiness.

Other antipsychotic medications (e.g., risperidone, quetiapine) have not been associated with significant benefit in anorexia nervosa [40,41]. Although several recent publications, including two case reports and two retrospective chart reviews, suggest that aripiprazole may benefit weight gain and psychopathology in anorexia nervosa, placebo-controlled studies have not been completed [42*,43,44*,45*]. A meta-analysis of seven small RCTs using SGAs (four trials with olanzapine, two trials with quetiapine, one trial with risperidone) pooled data from 201 patients with anorexia nervosa [46*]. Dold et al. concluded that there was a general lack of efficacy for BMI increases associated with SGAs [46*]. The pooled olanzapine data did show a greater change in BMI compared with placebo, although not statistically significant. These findings, together with the results from the larger olanzapine trial by Attia et al., (Attia EA, Eating Disorders Research Society Annual Conference 2016), contribute to a general consensus that olanzapine remains the only medication with some consistent evidence supporting a weight gain benefit in anorexia nervosa. The modest weight increase that appears to be associated with olanzapine does not change the general evidence base suggesting limited utility for medication as stand-alone treatment for anorexia nervosa. Olanzapine, if used, should be in conjunction with behavioral interventions that aim to help individuals with anorexia nervosa in achieving and maintaining a healthy weight range.

D-Cycloserine

Individuals with anorexia nervosa report significant fears of many specific foods. In the realm of anxiety disorders, D-cycloserine (DCS) has been found to be a useful adjunct to exposure therapy in the treatment of specific phobia. The application of this approach in the treatment of anorexia nervosa has yielded mixed results. A small (N = 11) RCT that examined DCS together with exposure therapy showed no significant benefit of medication [47]; alternatively, a more recent trial with 36 partial-hospital patients reported that DCS with four sessions of exposure therapy resulted in a 1.4-kg increase over 2 weeks, compared with a 0.2-kg increase with exposure therapy alone [48*].

Dronabinol

Dronabinol, a synthetic cannabinoid agonist used to treat loss of appetite, nausea, and vomiting, has
Medications to improve bone density

Bone health is impacted greatly by the undernutrition associated with anorexia nervosa. Affected individuals are at risk for osteopenia, osteoporosis, and higher fracture rates [51,52]. Alendronate treatment in 32 adolescents for one year was shown to have a significant effect on bone mineral density in femoral neck (but not lumbar spine) compared with placebo, although weight gain over that year was a better determinant of bone health than was medication [53]. Klibanski et al. [54] demonstrated lack of efficacy of oral estrogen replacement vs. placebo on bone health for adults with anorexia nervosa, suggesting that the high levels of hormone administered may have been suppressing other hormones (e.g., Insulin-like Growth Factor-1) needed for bone turnover. More recently, transdermal estradiol patches with cyclic progesterone have been tested to administer physiologic doses to adolescents with anorexia nervosa. Compared with placebo, this intervention significantly improved spine and hip bone mineral density in 110 adolescent girls with anorexia nervosa, while having no effect on weight [55]. Transdermal estrogen replacement has also been reported to significantly reduce trait anxiety scores on the Spielberger’s State-Trait Anxiety Inventory for Children in adolescents with anorexia nervosa, although similar effects on state anxiety, body shape perception, and eating attitudes were not found [56]. Results of a recently completed RCT examining the effect of teriparatide, an injected hormone replacement (NCT00759772). The use of hormone replacement is complex in individuals with anorexia nervosa as it masks hypothalamic dysfunction, and may contribute to patients underestimating their degree of illness severity; however, transdermal estrogen therapy and other interventions deserve additional study as decreased bone density is among the most serious and long-lasting effects associated with anorexia nervosa.

CONCLUSION

Eating disorders are serious and complex illnesses with physiological and behavioral manifestations.

Medications are clinically useful in the treatment of bulimia nervosa and BED, although they are often utilized in combination with targeted psychotherapy and other behavioral management strategies. SSRIs and other antidepressants are particularly useful in bulimia nervosa. For BED, medications associated with appetite and weight reduction, such as the stimulant LDX, have demonstrated success. Anorexia nervosa poses a greater treatment challenge as the medications useful for other eating disorders offer no significant benefit in anorexia nervosa. Olanzapine appears to have a small but significant effect on weight gain in anorexia nervosa, but should likely not be used as a stand-alone treatment.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

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The retrospective chart review, which examined the efficacy of olanzapine and aripiprazole as augmentation agents of SSRIs, cited an enhanced benefit for measures of psychopathology and with aripiprazole augmentation but not olanzapine. No significant effects associated with weight gain were found for either medication.


34. Frank GK, Aripiprazole, a partial dopamine agonist to improve adolescent and young adult outcomes in anorexia nervosa: a case series and literature review. The case series, which describes four adolescents with chronic anorexia nervosa, suggests some utility of aripiprazole for treatment of anorexia nervosa, although further research is necessary.


The retrospective review of 106 adolescent charts showed that aripiprazole was associated with greater BMI increases, although implications are limited because of lack of a randomized, controlled study design.


39. In contrast to the 2007 study by Steinglass et al. (47), this RCT provides preliminary evidence that d-cycloserine may be a useful adjunct to exposure therapy in improving weight gain in AN.


42. The study describes an increased intensity of exercise associated with dronabinol intervention in anorexia nervosa, which did not have significant negative impact on body weight.


