Pharmacologic Treatments for Binge-Eating Disorder

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Binge-eating disorder (BED) is the most common eating disorder and is associated with poor physical and mental health outcomes. Psychological and behavioral interventions have been a mainstay of treatment for BED, but as understanding of this disorder has grown, pharmacologic agents have become promising treatment options for some patients. At this time, only one drug—the stimulant prodrug lisdexamfetamine—is approved for the treatment of BED. Numerous classes of medications including antidepressants, anticonvulsants, and antiobesity drugs have been explored as off-label treatments for BED with variable success. Although not all patients with BED may be suitable candidates for pharmacotherapy, all patients should be considered for and educated about pharmacologic treatment options.

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Binge eating is defined as eating an unusually large amount of food in a short period of time with a sense of loss of control over eating. When these episodes occur frequently, cause significant distress, and are not associated with inappropriate weight loss behaviors, the individual may be experiencing binge-eating disorder (BED), which requires treatment to prevent poor physical and emotional outcomes.[1] The goals of treatment should be to reduce the frequency of binge-eating episodes, improve weight and metabolic health, and address dysfunctional thoughts and habits related to food as well as any depression or anxiety that may also be present.[2] While psychological and behavioral interventions have evidence supporting their efficacy as treatment for BED,[2–4] the focus of this article is pharmacologic agents.

RATIONALE FOR PHARMACOLOGIC TREATMENT

A growing body of research shows that some patients with BED can benefit from pharmacologic treatment.[2] Pharmacologic treatments for BED may be beneficial adjuncts to nonpharmacologic treatment for certain patients or appropriate as monotherapy for others. Some patients with BED may not respond to psychotherapy.[5] Other patients may not be willing to participate in psychological or behavioral interventions, and, for others, these types of treatments may be unavailable.[5,6] Other reasons for using pharmacologic treatment include the presence of comorbid psychiatric comorbidities or obesity.[5,6] Patients who meet any of these criteria should be considered possible candidates for pharmacologic treatment.

Research into the genetics and underlying neurobiology of BED has revealed abnormalities in a number of neurotransmitter systems, including opioid, dopamine, serotonin, and norepinephrine.[5] The compulsive eating associated with BED has also been compared to the compulsive behaviors seen in other addictive disorders, and, thus, dysfunctional reward circuitry may be involved.[7] The findings on potential biological causes of BED have provided therapeutic targets for researchers to investigate effective treatments.

PHARMACOLOGIC TREATMENT OPTIONS

Only one drug is currently approved by the US Food and Drug Administration for the treatment of BED—which is the stimulant prodrug lisdexamfetamine. Numerous agents from several drug classes have been investigated in clinical trials or used as off-label treatments for BED, and many have shown positive results. However, each agent has distinct strengths and limitations, and patients should be matched with the treatment most likely to address their unique needs.

Approved Treatment

Lisdexamfetamine has been approved to treat attention-deficit/hyperactivity disorder (ADHD) in children since 2007 and adults since 2008. It received approval for the treatment of moderate to severe BED in adults in 2015.[8] Lisdexamfetamine, a prodrug of dextroamphetamine, and other amphetamines facilitate dopamine and norepinephrine neurotransmission by blocking the reuptake of these monoamines into the presynaptic neuron and increasing their release into the extraneuronal space.[8,9] Compared with immediate-release stimulants, lisdexamfetamine has slower uptake into the brain, is longer acting, and may have reduced abuse liability.[8,9]

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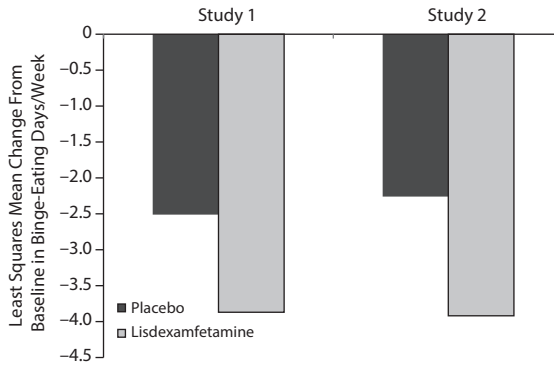
Figure 1. Change in Binge-Eating Days/Week After 11 to 12 Weeks of Treatment With Lisdexamfetamine[a]



[a]Data from McElroy et al.[13]

Clinical Points

- Select appropriate pharmacologic agents as part of a treatment plan designed to not only reduce binge-eating behavior but also address dysfunctional eating-related thoughts and behaviors, as well as any mood symptoms
- As part of a multidisciplinary treatment program, consider pharmacologic treatment for all patients with BED, but especially those who do not fully respond or are resistant to behavioral interventions or for whom behavioral interventions are unavailable
- Consider topiramate for patients with BED and comorbid substance abuse.

The rationale for using lisdexamfetamine in BED was based on several factors. One factor is that BED and ADHD frequently overlap and may share some underlying neurobiological or psychopathological features, including impulsivity.[10] In addition, lisdexamfetamine has been associated with decreased appetite and weight loss as side effects of treatment.[9] Although these may be adverse events in some patients with ADHD, they may benefit individuals with BED who are overweight or obese. Finally, dopamine and norepinephrine are involved in eating behavior and reward.[8] Genetic polymorphisms associated with abnormal dopaminergic signaling have been found in individuals who exhibit binge-eating behavior, and the binge-eating episodes, which often involve the consumption of highly palatable food, further stimulate the dopaminergic system.[11] This ongoing stimulation may contribute to progressive impairments in dopamine signaling.[11] Lisdexamfetamine is hypothesized to reduce binge-eating behavior by normalizing dopaminergic activity.[8]

My colleagues and I conducted an 11-week, phase 2 study[12] to determine if lisdexamfetamine was safe and efficacious for BED. We randomly assigned 260 adult patients who met *DSM-IV-TR* criteria for moderate to severe BED in a 1:1:1:1 ratio to receive placebo or a 30-, 50-, or 70-mg/d dose of lisdexamfetamine. All participants receiving lisdexamfetamine were started at a dose of 30 mg/d, and the higher doses were titrated over the first 3 weeks. Weeks 3 through 11 were a dose-maintenance period. The mean age of participants was 38.7 years, and most were white, female, and obese. Binge eating was assessed through clinician interview and daily patient diaries. At the completion of the study, we found a significant reduction in the number of binge-eating days per week in the groups receiving 50 mg/d and 70 mg/d of lisdexamfetamine ($P = .008$ and $P < .001$, respectively), but not in the 30 mg/d group ($P = .88$), compared with the placebo group. We found the safety profile of lisdexamfetamine in this population to be similar to that seen in adults with ADHD, with the most common side effects being dry mouth, decreased appetite, insomnia, and headache. Mean weight decreased among treatment groups but not in the placebo group.

This study was followed by 2 randomized, double-blind, multicenter, parallel-group, placebo-controlled phase 3 studies.[13] Both studies used identical designs and methods and lasted for 12 weeks. Participants were randomly assigned in a 1:1 ratio to receive placebo or lisdexamfetamine. Lisdexamfetamine was started at 30 mg/d, but, based on the results of our previous study,[12] all participants were titrated up to 50 mg/d, with the option of going up to 70 mg/d based on tolerability and clinical need. The first study enrolled 374 participants and the second enrolled 350. After 12 weeks, both studies found significant reductions in the number of binge-eating days per week in the active treatment group compared with placebo ($P < .001$ for both studies; Figure 1).[13] Lisdexamfetamine was also found to be superior to placebo on a number of secondary outcome measures including global improvement, binge-eating cessation for 4 weeks, and reduction of obsessive-compulsive binge-eating symptoms, body weight, and triglycerides. The side effects reported in these studies were similar to those of the phase 2 study (eg, dry mouth, insomnia, headache), and the discontinuation rates due to adverse events were 6.3% and 3.9%. No suicidality or misuse of the study drug was observed. Lisdexamfetamine is known to be associated with cardiovascular side effects, and increased pulse and small elevations in systolic and diastolic blood pressure were detected.[13] A meta-analysis[14] of the phase 2 and 3 trials of lisdexamfetamine found that the number needed to treat to reach response was 3 and to reach remission was 4, and the number needed to harm for discontinuation due to an adverse event was 44, which is a very favorable benefit/risk ratio.

Two long-term, phase 3 studies of lisdexamfetamine for BED have been conducted, and the data from these studies have been made available[15] but are not yet published. A 53-week open-label study[15] was designed to determine safety and tolerability of lisdexamfetamine during maintenance treatment of BED. The study began with a 4-week dose optimization period followed by 48 weeks of maintenance treatment and a 1-week follow-up. Lisdexamfetamine was found to be generally safe and well tolerated, with the most common side effects being similar to those reported during short-term treatment. A 39-week placebo-controlled, randomized, double-blind study[15] was conducted to

determine the maintenance of efficacy of lisdexamfetamine for BED. This study began with 12 weeks of open-label treatment followed by 26 weeks in which the patients who had met response criteria during the initial phase of the study were randomly assigned to either continue their current dose of lisdexamfetamine or be switched to placebo. A 1-week follow-up was also conducted. At the conclusion of the study, only 3.7% of the group receiving lisdexamfetamine had relapsed compared with 32.1% of those receiving placebo. Lisdexamfetamine was found to be significantly superior to placebo based on time to relapse ($P < .001$).[15]

Taken together, the results of these phase 2 and 3 studies indicate that lisdexamfetamine should be considered an appropriate option for acute and maintenance treatment of moderate to severe BED in adults. However, because of the side effect profile and potential for misuse of lisdexamfetamine, this agent should not be used in patients who also have bipolar disorder, drug or alcohol abuse, uncontrolled hypertension, or cardiovascular disease. In addition, many questions remain unanswered regarding the use of lisdexamfetamine for BED. Future studies need to determine how lisdexamfetamine compares to other BED treatments and whether it is effective for BED of mild severity or in children and adolescents. It is also unknown whether other stimulants or other nonstimulant ADHD pharmacotherapies might be effective for BED, although a small (N = 40) study of atomoxetine[16] suggested efficacy and tolerability versus placebo in BED.

Off-Label Treatments

The off-label treatments that have been the most thoroughly investigated as treatments for BED are antidepressants, antiepileptics, and antiobesity agents.[5]

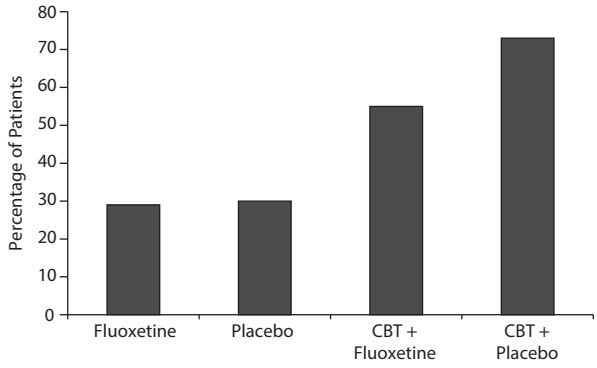
Antidepressants. Antidepressants have been explored as a treatment for BED for a number of reasons.[5] Antidepressants have been found to reduce binge eating in bulimia nervosa, and they are effective for many disorders that frequently occur with BED such as major depressive disorder, generalized anxiety disorder, and obsessive-compulsive disorder.[5] Furthermore, antidepressants target neurotransmitters that are thought to be disrupted in BED, such as dopamine and norepinephrine.

Evidence supports a modest effect of antidepressants on binge eating but not on weight. Stefano and colleagues[17] conducted a meta-analysis of 7 randomized placebo-controlled trials of antidepressants for the short-term treatment of BED. One trial investigated the tricyclic antidepressant imipramine, but the other 6 studied selective serotonin reuptake inhibitors. The meta-analysis found a significantly higher rate of remission among the groups receiving antidepressants compared with those receiving placebo (40.5% vs 22.2%, $P = .003$). The meta-analysis did not find antidepressants to be significantly more effective than placebo for reducing weight or the frequency of binge-eating episodes, and the rates of treatment discontinuation between the 2 groups were comparable.[17]

The meta-analysis[17] also found that the groups receiving antidepressants experienced a significantly greater improvement in depressive symptoms than those receiving placebo ($P = .03$). This finding is important because BED and depression are frequently comorbid. Guerdjikova and colleagues[18] have conducted the only study specifically investigating the treatment of patients with BED and comorbid depressive disorder. Forty patients meeting *DSM-IV-TR* criteria for BED and a comorbid depressive disorder were randomly assigned to receive either the antidepressant duloxetine or placebo. After 12 weeks, the group receiving duloxetine experienced greater reductions in mean number of binge-eating days per week ($P = .04$), weekly frequency of binge-eating episodes ($P = .02$), weight ($P = .04$), and global severity of both BED ($P = .02$) and depressive illness ($P = .01$).[18] Thus, for patients with BED and a comorbid depressive disorder, antidepressants should be considered as treatment options, but an antidepressant that is not associated with weight gain should be selected. Although bupropion is associated with weight loss, it was not found to be effective for BED in a small (N = 61) placebo-controlled study[19]; however, it was well-tolerated, and in my practice I consider it as a medication option for patients with BED who have comorbid obesity and/or depression.

Despite evidence of some beneficial effect on BED, antidepressants have several limitations.[5,17] No data on long-term effectiveness of these agents are available, and the results of short-term trials are limited by high placebo response rates.[5] Furthermore, antidepressants may be no more effective than behavioral treatments. A study by Grilo et al[20] compared 108 patients with BED who were randomly assigned to receive fluoxetine, placebo, cognitive-behavioral therapy (CBT) plus fluoxetine, or CBT plus placebo. Both of the groups receiving CBT experienced greater rates of remission (no binge episodes for 28 days) than the fluoxetine-only and the placebo groups, but no significant difference was found between the CBT plus fluoxetine and the CBT plus placebo group (Figure 2).[20] At 12-month follow-up[21] (which did not include the placebo-only group), remission rates for the CBT-plus-fluoxetine and CBT-plus-placebo

Figure 2. Remission[a] Rates After 16 Weeks of Treatment With Fluoxetine or Cognitive-Behavioral Therapy (CBT) for Binge-Eating Disorder[b]



[a]Remission was defined as 28 days with no binges.
[b]Data from Grilo et al.[20]

groups did not differ significantly ($P = .57$), but both differed from fluoxetine-only ($P = .024$ and $P = .005$, respectively). A similar study by Devlin and colleagues[22] also found CBT to be more effective than fluoxetine for reducing binge-eating episodes in 116 adults who were also receiving group therapy for weight control. Antidepressants, therefore, may not be more effective than behavioral interventions such as CBT and may not enhance the efficacy of CBT.

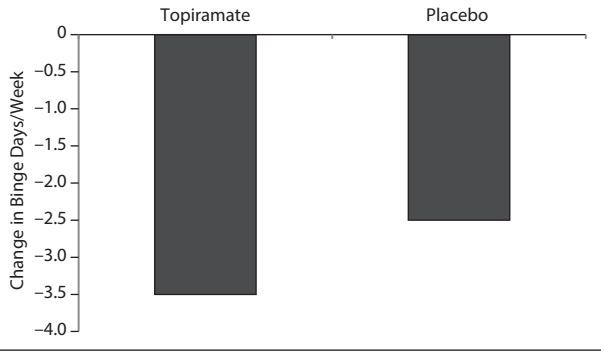
Antiepileptics. As with antidepressants, many factors led to the investigation of antiepileptic medications for BED. Antiepileptics are prescribed to treat psychiatric disorders more often than they are prescribed for epilepsy, and many of the disorders that respond to these drugs frequently occur comorbidly with BED, including mood and substance use disorders.[5,23] Many antiepileptic drugs are known to affect weight, and some are associated with weight loss[5,24]; antiepileptics' mechanisms of action affect peptide and neurotransmitter systems that are known to be involved in appetite, craving, and feeding behavior.[5,25] The antiepileptics lamotrigine, phenytoin, and oxcarbazepine have been tested in BED or related conditions but have shown negative or conflicting results.[5] The antiepileptics topiramate and zonisamide, however, have been found to be effective for BED.[5]

Topiramate is the antiepileptic that has received the most study as a treatment for BED. My colleagues and I conducted a 14-week randomized, placebo-controlled trial[26] to assess the safety and efficacy of topiramate for BED in 61 participants who were obese and met diagnostic criteria for BED. At endpoint, the patients receiving topiramate had a significantly greater reduction in binge-episode frequency than those receiving placebo (94% vs 46%; $P < .02$). The topiramate group also experienced greater reductions in binge-eating days per week, weight, and overall severity of BED symptoms. My colleagues and I conducted a larger, multicenter, 16-week study[27] that enrolled 407 patients, and we were able to replicate our findings that topiramate was efficacious for reducing weight and the symptoms of BED (Figure 3).[27]

The patients who completed the single-center study[26] were given the opportunity to enroll in a 42-week, open-label trial of topiramate.[28] Thirty-one patients enrolled, but only 10 patients completed the trial. While the results suggested long-term efficacy of topiramate for some patients with BED and obesity, discontinuation due to adverse events was common.

Claudino and colleagues[29] conducted a randomized, placebo-controlled trial to investigate whether topiramate could enhance the effect of CBT for reducing weight and binge eating in BED. The 21-week study enrolled 73 participants who were considered obese due to a body mass index (BMI) ≥ 30 kg/m^2 and met criteria for moderate to severe BED. The CBT plus topiramate group experienced significantly greater reductions in weight and binge-eating behavior than the CBT plus placebo group ($P < .001$ for both).[29] The results of this study are noteworthy because, whereas antidepressants do not appear to enhance the efficacy of CBT, topiramate does seem to enhance the effect of CBT. Topiramate can be considered as an adjunctive treatment for patients with BED who are responding to CBT but may need more aggressive treatment to further resolve symptoms or induce weight loss.

Figure 3. Change in Binge-Eating Days/Week After Treatment With Topiramate[a]



[a]Data from McElroy et al.[27]

Unfortunately, the use of topiramate is somewhat limited by its side effect profile. Common adverse events reported during treatment with topiramate are paresthesia, upper respiratory tract infection, somnolence, nausea, taste perversion, dry mouth, pain, headache, and confusion.[26–29] On the other hand, topiramate has been shown to be efficacious in alcohol dependence, and therefore is an option for the BED patient who has a comorbid substance use disorder.[30,31]

The antiepileptic zonisamide was investigated in a 16-week, randomized, placebo-controlled trial of 60 obese patients with BED.[32] After treatment, the patients who received zonisamide experienced a significantly greater reduction in binge-eating episode frequency ($P = .021$), body weight ($P < .001$), BMI ($P = .001$), and overall illness severity ($P < .001$) versus placebo. Although zonisamide was efficacious, it was not well tolerated; discontinuations occurred due to psychological and cognitive complaints as well as injuries with bone fracture. Ricca and colleagues[33] conducted a small open study comparing CBT with CBT plus zonisamide in 52 patients with a diagnosis of BED or subthreshold BED. Patients were assessed at baseline, after 24 weeks when treatment ended, and 1 year after treatment ended. At 24 weeks, the CBT-plus-zonisamide group exhibited greater reductions in BMI ($P < .001$) and Binge Eating Scale scores ($P < .05$) than the CBT-only group. One year after treatment had ended, the CBT-plus-zonisamide group had greater reductions in binge-eating frequency ($P < .01$) and Binge Eating Scale scores ($P < .01$) than the CBT-only group.[33] Although the validity of these results is somewhat limited because this was a small, open study, zonisamide might be effective for enhancing the efficacy of CBT in BED.

Obesity treatments. Because BED and obesity are closely related, using antiobesity agents to treat BED would seem like a logical treatment strategy. The antiobesity medications fenfluramine and sibutramine both showed evidence of

efficacy in BED, but both of these agents have been removed from the market because of serious safety concerns.[5]

Orlistat is an approved weight loss medication with a mechanism of action that is different from those of other agents used in BED. Whereas other agents such as stimulants, antidepressants, and antiepileptics that have shown efficacy in BED act on neurotransmitter systems, orlistat does not act on the central nervous system. Orlistat promotes weight loss by partially inhibiting dietary fat absorption.[34] Golay and colleagues[34] conducted a placebo-controlled trial of orlistat in 89 patients with BED and BMIs in the obese range. All participants were also told to follow a restricted-calorie diet. After 24 weeks of treatment, the group receiving orlistat had lost a significantly greater amount of weight than the placebo group ($P = .0001$). Although fewer patients in the orlistat group met criteria for BED at the end of treatment compared with the placebo group, the difference was not statistically significant.[34] Grilo and colleagues[35] conducted a trial in which 50 patients with BED and obesity were randomly assigned to receive guided self-help CBT plus either placebo or orlistat. After 12 weeks of treatment, a significantly greater percentage of the CBT-plus-orlistat group achieved BED remission compared with those in the CBT-plus-placebo group (64% vs 36%; $P = .048$). A significantly greater percentage of the orlistat-treated group also achieved a loss of 5% or more of body weight (36% vs 8%; $P = .017$).[34] Adverse effects reported were gastrointestinal events related to mechanism of action. Thus, although orlistat may not be an effective monotherapy for BED, this agent may be a useful adjunct for patients who have managed to reduce binge frequency with CBT but have been unable to lose weight. Clinicians must monitor for misuse, however.[36] If patients begin to use orlistat as a means of compensating for bingeing, then the BED diagnosis would evolve into bulimia nervosa.

Experimental Treatments

Numerous agents from diverse drug classes have been tested in BED with mixed results. Acamprosate and baclofen are both drugs that are used to help control alcohol cravings; therefore, investigators hypothesized that they may be effective for controlling the cravings that lead to binge eating.[37,38] In a small (N = 40) randomized, placebo-controlled trial,[37] acamprosate was associated with improvements in binge-day frequency and measures of obsessive compulsiveness of binge eating, and food craving. Baclofen was found to be associated with reduced binge-eating frequency, but also with increased depression symptoms, in a small (N = 12) randomized, placebo-controlled trial.[38]

Because eating behavior, reward, and addiction are known to involve the endogenous opioid system, opioid antagonists have been explored as potential treatments for BED.[5] A small (N = 33) trial[39] of naltrexone (which is approved to treat alcohol and opioid use disorders) in patients with binge eating and obesity showed reduced binge-eating frequency, but the effects did not differ significantly from placebo; however, case reports have been favorable.[5] A combination of naltrexone and bupropion is approved for weight loss. My colleagues and I conducted a study[40] in which 25 women with major depressive disorder who were obese/overweight received treatment with the combination of naltrexone and bupropion plus dietary and behavioral counseling. Treatment was associated with reductions in binge-eating symptoms, weight, food craving and appetite, and depressive symptoms. A pilot study[41] (N = 62) was conducted of the novel opioid receptor antagonist ALKS-33 in BED and obesity, but this agent failed to separate from placebo. However, in a randomized, placebo-controlled study of an intranasal formulation of the opioid antagonist naloxone (indicated for emergency opioid overdose reversal),[42] the patients treated with naloxone experienced significant reductions in time spent binge eating ($P = .024$), BMI ($P = .015$), and their desire to binge eat ($P < .001$) compared with the patients who received placebo.

Antiobesity agents continue to be investigated in BED. The injectable drug liraglutide plus diet and exercise counseling was found to be significantly superior to diet and exercise counseling alone for reducing binge-eating symptoms and obesity in a pilot study (N = 44),[43] and positive outcomes have been reported in 2 cases in which patients with BED were treated with phentermine-topiramate combination.[44]

GENERAL PRINCIPLES AND CONCLUSIONS

Effective treatment of BED is essential because BED is the most common eating disorder and leads to considerable distress, poor health outcomes, and reduced quality of life. For various reasons, some patients may receive only psychological or behavioral interventions while others may receive pharmacologic treatment, but the most effective treatment regimen may be a combination of both behavioral and drug interventions.[45] All patients with BED should be informed that pharmacotherapy is an option, but because pharmacologic treatment of BED is an emerging area and no guidelines are widely accepted, clinicians must proceed cautiously. All patients must be carefully assessed for psychiatric and medical comorbidity, and these findings should guide treatment selection. Multidisciplinary treatment that involves a primary care physician, a psychiatrist, a psychotherapist, and a dietitian may be necessary for resolving all of the symptoms of BED and teaching patients how to maintain a healthier lifestyle.[46,47] Research into additional treatments for BED is ongoing, so new treatments will likely continue to become available. With effective treatment, patients with BED should be able to overcome their binge eating and improve their overall health and emotional well-being.

Drug names: acamprosate (Campral and others), atomoxetine (Strattera and others), baclofen (Lioresal, Gablofen, and others), bupropion (Wellbutrin and others), duloxetine (Cymbalta and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), lamotrigine (Lamictal and others), liraglutide (Saxenda, Victoza), lisdexamfetamine (Vyvanse), naloxone (Narcan and others), naltrexone (Revia, Vivitrol, and others), naltrexone/bupropion (Contrave), orlistat (Alli, Xenical), oxcarbazepine (Trileptal, Oxtellar, and others), phentermine/topiramate (Qsymia), phenytoin (Dilantin, Phenytek, and others), sibutramine (Meridia), topiramate (Topamax, Qudexy, and others), zonisamide (Zonegran and others).

Disclosure of off-label usage: Dr McElroy has determined that, to the best of her knowledge, acamprosate, atomoxetine, baclofen, bupropion, duloxetine, fenfluramine, fluoxetine, imipramine, lamotrigine, liraglutide, naloxone, naltrexone, naltrexone/bupropion, orlistat, oxcarbazepine, phentermine/topiramate, phenytoin, sibutramine, topiramate, and zonisamide are not approved to treat binge-eating disorder.

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