Binge Eating Disorder: A 5-Year Retrospective Study on Experimental Drugs

Michelle N Levitan1,2
Marcelo Papelbaum2
Mauro G Carta3
Jose C Appolinario1
Antonio E Nardi1
1Psychiatry Institute/Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; 2Eating Disorders Department/Sheba Medical Center, Ramat Gan, Israel; 3Dipartimento di Scienze Mediche e Sanità Pubblica, Università Degli Studi di Cagliari, Cagliari, Italy

Abstract: Binge eating disorder (BED) affects a significant rate of the general population causing a negative impact on their quality of life, weight, and self-esteem. Besides psychological treatments that compose the majority of the studies, pharmaceuticals have contributed to improve a host of clinical parameters, thus being an important component of the treatment. We opted to target the latest results by performing a review of the literature on the pharmacology for BED from the last 5 years. To achieve this goal, the terms: “binge eating disorder” and “treatment” were added to the PubMed database and the website clinicaltrials.gov. At least five drugs were either being tested or had already been recognized to improve BED symptoms — although only lisdexamfetamine is currently approved by the FDA to treat this condition. However, due to a better understanding of BED psychopathology in the last decade, it is notorious that improvement of eating-related symptoms is not the only desired target. Due to the significant comorbidity percentage (30%), weight loss is highly pursued, as well as the amelioration of clinical parameters which highlights the importance of having new agents combining both objectives.

Keywords: binge eating disorder, treatment, pharmacological treatment

Introduction

Binge eating disorder (BED) is the most prevalent eating disorder (ED), with estimates of 2–5% of the general adult population, although its recognition as a single diagnosis only occurred in 2013 by the Diagnostic and Statistical Manual of Mental Disorders (DSM), fourth edition. In its latest edition, BED is defined by recurrent episodes of eating unusually large amounts of food while experiencing a feeling of losing control in the absence of regular use of inappropriate compensatory behavior. Marked distress regarding binge eating is present and the binge episodes occur, on average, at least 1 day a week for 3 months.1

Lifetime prevalence of BED ranged from 1.2% to 4.5% (when included subthreshold BED) and was noted to be more similar between men and women when compared to the distribution as observed with anorexia and bulimia nervosa.2 Typically, its symptoms begin during childhood and adolescence, but it can also be seen in the elderly with longer duration of illness reported.2 A previous study has shown a 12-month persistence of 44.2%, meaning that half of the patients could have achieved spontaneous remission on the course of the disorder.3 However, it can also assume an intermittent behavior.

Medical and psychiatric comorbidities are commonly observed in individuals with BED. At least one core DSM-5 disorder can be found co-occurring in up to
80% of BED patients, mainly depression and anxiety disorders, although other psychiatric disorders, including bipolar disorder, borderline personality disorder, and substance abuse have also been found to be related to BED.\textsuperscript{4,5} However, its association to general psychopathology, the presence of clinical comorbidity must not be forgotten. Higher prevalence rates of BED are found in overweight and obese individuals,\textsuperscript{6} and indeed, the presence of psychopathology as associated to obesity seems to be more severe in the presence of BED.\textsuperscript{7} Also, individuals with BED have an increased risk to develop type 2 diabetes, are more likely to develop nonalcoholic fatty liver disease, gastrointestinal problems, and disrupted sleep. An even higher prevalence was noted among infertile women.\textsuperscript{8,9}

Previous studies have found impaired quality of life (QL) in individuals with BED. In addition, obese individuals with BED have shown reduction in QL when compared to non-obese BED patients. For instance, when using the Medical Outcomes Short Form-36 Health Survey (SF-36) to estimate QL, obese BED patients showed lower scores in comparison to the non-obese BED sample (45.3 [9.6] vs 53.6 [9.4], respectively, \(P = 0.001\)).\textsuperscript{10} Interestingly, obesity seemed to impact more on the physical variables of QL while BED was linked with poorer mental health and social functioning. Particularly, both the presence of depressive symptoms and a poor body image attitude seemed to objectively impact BED-QL.\textsuperscript{11}

Despite its high prevalence rate and common association to clinical and other psychiatric problems, BED patients commonly remain either undiagnosed or receive inadequate treatment.\textsuperscript{12} Frequently, BED patients are referred to treat medical comorbidities without specialized eating disorder (ED) treatment.\textsuperscript{13} Considered underestimated in comparison to other frequently psychiatric complaints, such as depressive and anxiety-related symptoms – which may culminate into inadequate psychological or pharmacological treatment choices.

Before considering BED treatment, an extensive evaluation should be made in order to identify and estimate problems in the 3 main areas of concern, namely, eating-behavior and related psychopathology, general psychological and psychiatric disorders, and presence of obesity with other medical problems possibly associated with BED.\textsuperscript{14} As a result, treatment algorithms should reflect the hierarchy and severity of problems in each individual area and should include the choice of different strategies that may include nutritional, psychological and pharmacological treatments. The American Psychiatric Association recommends a multidisciplinary approach that includes psychological treatment as a main approach and considerations for medication as adjunctive therapy.\textsuperscript{15} In contrast, the National Institute and Care Excellence also includes the possibility of medication monotherapy.\textsuperscript{16} However, both guidelines do not clarify which specific best practices of weight management should be offered, including dieting-based approaches, medication or even bariatric surgery.

A recent meta-analysis concluded that among BED adults, there is strong evidence that favors the use of cognitive-behavior therapy (CBT) and medications that include lisdexamfetamine (LDX), second-generation antidepressants, sibutramine (discontinued in many countries mainly due to cardiovascular risk) and topiramate. However, several limitations were found, which included methodological issues, fewer reports of adverse effects and discontinuation of drug trials, and the heterogeneity of outcomes.\textsuperscript{17} In this last regard, an optimal treatment related to eating, general psychopathology, and obesity severity is still required for a subset of patients.

Considering the lack of evidence on sufficient drug efficacy and the urge for new approved treatment options, this paper aimed to update recent pharmacological treatment data for BED by using the last 5 years as a timeframe. Reviews including interventions with previous timeframes had already been published and showed benefits of pharmacological treatment for BED. For instance, a previous meta-analysis that included 33 placebo-controlled trials showed a significant advantage of the pharmacological treatment over placebo for achieving short-term remission from BED (48.7% vs 28.5%).\textsuperscript{18} Despite that, only one agent emerged as an approved drug for BED treatment. Since 2015, when LDX received approval from the US Food and Drug Administration (FDA) for moderate/severe BED treatment in adults, no other medications have been approved and, in general, they have solely been used in an “off label” fashion. It is important to take into consideration the adverse effects that often lead to discontinuation: dry mouth, decreased appetite, insomnia and headache.

Pharmacological BED treatment in clinical practice usually follows hierarchic principles related to the patient’s complaints, the physician’s evaluation and findings in physical examination or laboratory. Evaluation on each potential drug treatment for BED should be done taking into account clinical and psychiatric aspects, that may argue against the use of specific agents. Considering
the importance to explore recent data on pharmacological trials on BED (including those that investigated new promising agents in order to point out to the best options available and future directions to remission achievement), this review was performed and condensed in Table 1. To enrich our findings, we also included sections related to novelty treatments for BED based on animal studies and advantages of each medication regarding adverse events.

Pharmacodynamics of BED

In order to allow for a better understanding of the drugs’ role in BED, some neuromechanisms associated to a possible development and maintenance are exposed. In fact, many neurotransmitters, hormones and agents seem to be involved in BED induction and maintenance of BED. Below are listed some of the most significant findings related to this topic.

Neurotransmitters

When BED is evaluated in the light of impulsive/compulsive food consumption theory, and its regulation by the brain rewards system hypotheses, dopaminergic neurotransmission seems the most appealing neuromechanism to explore. In this model, the dopaminergic release, possibly due to an altered function in cortical and striatal regions, would otherwise be associated to motivational and control aspects of feeding (i.e., impulsivity/compulsive behaviors).

Following a different neuropsychological path in accordance by many authors, the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]), would be considered to have a key role in ED development. To support this hypothesis, studies show that serotonin is derived exclusively from dietary tryptophan, an essential amino acid. In excessive dieting and food restriction, a significant reduced ratio of tryptophan is found (mostly in anorexic patients). Furthermore, alterations on serotonin are associated to perfectionism and mood regulation. In a small study with obese binge eaters and non-obese binge eaters, decreased 5H-T transporter binding in the midbrain was found in the first group but not in the second.

An agent with these properties, vortioxetine, was also tested for BED treatment. This substance is a serotonin stimulator which also increases noradrenaline, dopamine, and acetylcholine in certain areas of the brain, as well as modulating γ-aminobutyric acid and glutamate neurotransmission. More details of this study will be discussed later in this article.

Hormones

Glucagon-like peptide-1 (GLP-1) is a hormone secreted from the small intestine in response to food ingestion. It can regulate food intake by slowing gastric emptying and through appetite inhibition in the brain thus reducing activation in appetite-related brain regions (possible brain areas involved: vagus nerve, nodose ganglia, hypothalamic nuclei, and the brain stem). Liraglutide, a GLP-1 receptor agonist, has been recently also approved for obesity management as an adjunct to physical activity and diet recommendations. It was previously approved in the type-2 diabetes treatment due to its effects associated with releasing insulin from the pancreas and decreasing glucagon release.

Oxytocin, another important hormone receiving attention in the last years, seems to play a strong effect on food consumption. Besides its anxiolytic properties and cortisol reactivity towards food, oxytocin appears to be also implicated in regulating reward-driven eating. This last hypothesis would be linked by the down-regulation of neural circuits related to the addictive theory of BED and bulimia nervosa.

Central Nervous Stimulant

The two following agents, LDX and dasotraline used for ADHD treatment, were also tested for BED due to their co-occurrence, high levels of impulsivity in BED and growing findings, therefore suggesting that binge eating is associated with the dysfunction of dopamine and/or norepinephrine neurotransmission.

Abbreviated from l-lysine-dextroamphetamine, LDX is a novel prodrug of dextroamphetamine (d-amphetamine) linked to the amino acid l-lysine, itself inactive and metabolized by mechanisms associated with red blood cells. With LDX hydrolysis, there is an inhibition of the reuptake of dopamine and norepinephrine from the synaptic cleft which simultaneously enhances the release of both, besides serotonin.

Additionally, there is dasotraline, a novel dual-acting dopamine and norepinephrine re-uptake inhibitor which is the only drug being currently tested in trials for BED treatment. Following developments with LDX, methylphenidate is another psychostimulant used for ADHD and presumed to exert its effects by means of dopamine transporter blockade and is overall well tolerated by patients with low levels of treatment attrition. At last, although not a psychostimulant per se, we present a study with BED
| Publication date | Investigational drug | Type of study                      | BED evaluation                           | Dosage (mg/day) | Sample size | Main outcomes                                                                 | Main findings                                                                 | Weight loss evaluation                                                                 |
|------------------|---------------------|-----------------------------------|------------------------------------------|-----------------|-------------|----------------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| 2015             | Armodafinil         | 10-week randomized placebo-         | DSM-IV-TR criteria (and BMI ≥ 25kg/m2); 150-250 mg/d | n=60            |             | BE episodes                                          | Higher but not statistically significant decrease of BE episodes in the clinical group (26% vs 21%) | Weight and BMI did not change significantly over time in either group.               |
|                  |                     | controls trial                     | number of BE episodes per week            |                 |             | per week and weight reduction                        |                                                                            |                                                                                     |
| 2015             | Disulfiram          | 11-week multicenter, randomized,   | DSM-IV-TR criteria (and BMI ≥ 25kg/m2)    | Randomization (1:1:1:1) to receive placebo or 30, 50, or 70 mg/d | n=63 (PLB) / n=196 (LDX groups) | Number of BE episodes per week                              | Change from baseline on BE days per week was significantly decreased in the 50- and 70-mg/d treatment groups but not in the 30-mg/d treatment group compared with the PLB group | Reduction in body weight was greater for all treatment groups compared with the PLB group at week 11 (all, P < .001) |
| 2015             |                     | double-blind, forced dose         |                                           |                 |             | based on clinician interview and self-reported BE diaries |                                                                            |                                                                                     |
|                  |                     | placebo-controlled clinical trial  |                                           |                 |             |                                                                                     |                                                                            |                                                                                     |
| 2015             | Liraglutide         | 16-week open trial                 | DSM-IV-TR criteria (and BMI ≥ 25kg/m2)    | 250 mg/d for 6 weeks | n=12        | Reduction in BES score, changes in the food craving, self-reported diaries and clinical global impression | All patients reduced the frequency of BE episodes 7.9 ± 1.2 to 0.9 ± 0.6 (p < .001) | Weight change: (92.8 ± 2.9 kgs to 90.4 ± 3.4 kgs p<0.01); CGI-S= 4.1 ± 0.2 to 1.1 ± 0.1 (p<0.01); food cravings= 37.3 ± 2.8 to 27.9 ± 1.9 (p<0.001) |
|                  |                     |                                   |                                           |                 |             |                                                                                     |                                                                            |                                                                                     |
| 2015             |                     | Randomised, prospective,          | BES score ≥ 18 (with obesity)             | 1.8mg/day (n=21) / control group with diet and exercise (n=21) | n=44        | Reduction in BES score                                  | Reduction on BES scores on Liraglutide group from 20 (IQR 18-27) to 11(IQR 7-16), p < 0.001 | Weight change: (94.54 ±18.14kg to 90.14±19.70kg, p<0.001) / 50% of the liraglutide group achieved a 5% weight reduction |
### 2016

**Lisdexamfetamine**
- 12-week two randomized parallel-group, multicenter studies
- DSM-IV-TR criteria and (≥ 3 binge eating days/week for 2 consecutive weeks before baseline and a CGI-S score ≥ 4 at baseline)
- Week 1: LDX 30 mg/d / Week 2: 50 mg/d / During weeks 3–4: increases to 70 mg/d based on tolerability and clinical need
- Study 1: n=383 / Study 2: n=390
- Change from baseline in BE days per week at weeks 11–12
- Change from baseline favored LDX for both studies (study 1: −1.35 [−1.70, −1.01], P<0.001; effect size [95% CI], 0.83 [0.60, 1.05]; study 2: −1.66 [−2.04, −1.28], P<0.001; effect size [95% CI], 0.97 [0.72, 1.21])

### 2017

**Lisdexamfetamine**
- Phase 3, multicenter, open-label, 12-month extension study
- DSM-IV-TR criteria and EDE-Q
- 4 weeks of LDX dose optimization followed by 48 weeks of LDX dose maintenance (50-70 mg/d)
- n=509
- Change from baseline in EDE-Q scores and BE per day for the past 28 days
- Mean EDE-Q global and subscale scores and the number of BE days for the past 28 days were lower than those at baseline (primary outcome were safety and tolerability)
- Greatest mean (SD) weight decrease was achieved at week 44, corresponded to an 8.67% (7.848%) decrease from baseline, after which weight remained stable.

**Lisdexamfetamine**
- 12-week open-label followed by a phase 3, double-blind, placebo-controlled, randomized withdrawal study
- DSM-IV-TR criteria and EDE-Q / ≥ 3 binge-eating days per week
- 50 mg or 70 mg adjusted during open-label phase
- n=411 (open-label phase) / n=275 (double-blind phase)
- Change in number of BE days per week
- Mean number of BE days per week reduced from 4.76 (1.21) to 0.13 (0.27) at open-label phase / Relapse criteria was 32.1% with placebo and 3.7% with LDX (P<0.001)
- Weight change (kg) on open-label phase: -5.43(4.26)

### 2017

**Naltrexone + Bupropion**
- Single-center, open-label, single-arm 24-week prospective study
- BES scores
- Combination therapy with 32 mg/day naltrexone ER and 360 mg/day bupropion ER
- n=23 (women)
- Changes in BES and CoEQ scores in a treated sample of overweight/obese subjects with MDD
- At week 24: CoEQ scores reduced to -41.8 (-59.2, -24.5; p<0.001) / 83% of subjects exhibited “little or no problem” according to BES severity / BES scores correlated to MADRS scores at week 12 (r = 0.54, p<0.05), but not to weight loss
- Weight Loss at week 24: -9.2% (-12.9, -5.4; p<0.001)

(Continued)
| Year | Drug            | Study Design                  | DSM-IV-TR Criteria and EDE-Q | Duration | n=10 (obese) | Change in weight | Weight Loss | BE Days and Episodes | Weight Loss | BE Days and Episodes | Weight Loss |
|------|----------------|-------------------------------|-----------------------------|----------|--------------|------------------|-------------|----------------------|-------------|----------------------|-------------|
| 2018 | Phentermine-Topiramate | Open-label, prospective, 12-week trial. | 2 weeks with 3.75 mg-23 mg/d and 2 weeks of 7.5mg-46 mg/d | n=10 (obese) | Change in weight | Significant reduction on weight (p<0.001); ES= 0.22 and in the BES (p<0.001); ES=2.41 | Average weight loss for all participants on PHEN/TPM-ER of 6.4% . When crossed over to placebo, was a weight regain of 1.5%.BED patients lost an average of 6.2 kg (SD = 3.7) while on PHEN/TPM-ER (baseline = 90.8 [SD = 18.3] kg) compared to an average loss of 4.4 kg (SD = 2.4) for BN patients (baseline = 64.6 [SD = 9.1]) | 2019 | Oxytocin | Double-blind, placebo controlled crossover study | DSM-5 criteria | 64UI intranasal oxytocin divided in 2 weeks of application | 25 women with BN or BED and 27 women weight matched women without ED | No significant effect on weight |
| 2019 | Phentermine-Topiramate | 12-week randomized placebo crossover trial | EDE-Q | (3.75 mg-23mg to 15mg-92mg) followed by 2 weeks of wash out and then crossover | BED patients=18 BNpatients=4 | BE days and episodes in 4 weeks | BE days in a 4-week period were 16.2 (SD = 7.8) days at baseline, 4.2 (SD = 8.4) days after PHEN/TPM-ER, and 13.2 (SD = 9.1) days after placebo (p < .0001). Reduction of BE days by 7.3 days (95% CI: −10.4 to −4.2; ES = 0.93) | 2019 | Methylphenidate | 12-week randomised trial of methylphenidate vs CBT in adult women | Binge episodes per week and changes in BMI | Initial dosage of methylphenidate was 18 mg/day, increased to 36 mg/day at Week 1, 54 mg/day at Week 2, 72 mg/day at Week 3, and 72 mg/day at Week 4, as tolerated | medication=22 CBT=27 | Changes in BMI and BE episodes | Both interventions were associated with decrease in BE episodes | Methylphenidate was associated with greater decreases in BMI from week 0 to week 12 = 5.18, p < 0.001; |
| Year | Treatment | Study Design | Inclusion Criteria | Maintenance Dose | n | Outcome Measures | Treatment Outcome |
|------|-----------|--------------|--------------------|-------------------|----|------------------|-------------------|
| 2020 | Vortioxetine | 12-week double-blind, placebo-controlled pilot study (1:1 fashion) | BED per DSM-5 criteria for at least a year (at least 3 BE days per week for the 2 weeks before the baseline visit) | 10mg/day for one week, then increasing to 20mg/day | 80 | Number of BE episodes per week | Both vortioxetine and placebo treatment were associated with significant reductions in binge eating frequency | Weight and BMI did not change significantly over time in either group |
| 2020 | Dasotraline | 12-week double-blind treatment with dasotraline | DSM-5 criteria | Fixed dose: 4mg/d and 6mg/d | 486 | Change in number of BE days per week | Reduction BE days in the 6mg group vs. PLB (-3.5 vs. -2.9; P=0.0045), but not significant on the 4mg group when compared to PLB | N/E |
| 2020 | Dasotraline | 12-week double-blind flexible-dose treatment | Moderate-to-severe BED based on DSM-5 criteria | Flexible dose (4-8mg/d) | 317 | Number of BE days per week and Changes in BE-CGI-S score and the Y-BOCS-BE | Reduction in BE days per week in dasotraline group vs. placebo (-3.74 vs. -2.75; P<0.0001); Y-BOCS-BE total score change for dasotraline vs. PLB (-17.05 vs. -9.88; P<0.0001) . Week 12 (LOCF), for dasotraline and placebo, 52.3% and 18.4% of patients, respectively, had a BE-CGI-S score of 1 (“not ill at all”) | Weight reduction ≥5% was observed in 45% of obese patients with a BMI ≥30 in active drug group (vs. 4.1% on placebo)* |
| 2020 | Naltrexone + Bupropion | 16-week open-label trial | DSM-5 criteria (with obesity) | 1 tablet a day up to a maximum of 2 tablets twice a day after the third week of prolonged-release tablets containing 8 mg of naltrexone HCl and 90 mg of bupropion HCl | 17 (BED group) / 20 (non-BED control group) | Changes in EDE-Q and BES scores | Among BED patients, EDE-Q Eating Restraint significantly increased (p = 0.031) and BES score significantly decreased (p = 0.04) | Overall, 85% of patients lost at least 5% of their body weight at 16 weeks, with an average mean of 8% weight loss. |

Note: *The same sample.

**Abbreviations**: CGI, clinical global impression; DSM, Diagnostic and Statistical Manual; BED, binge eating disorder; BES, binge eating scale; EDE-Q, eating disorders.
and armodafinil. This agent presents waking-promotion actions similar to the agents cited above and has psychoactive and euphoric effects. It is an indirect dopamine receptor agonist.

**Opiate Antagonists**

The use of agents such as naltrexone for BED is based on the model of an association between eating behavior and substance abuse. Considering that opioid system dysregulation underlies addictive binge eating, blockade of opioid receptors would diminish food intake and food craving – thus being a form of anticipatory reward regulated by endogenous opioid and mesolimbic dopaminergic systems.  

**Carbamates (Anti-Drug Abuse)**

Carbamates (disulfiram) act by inhibiting aldehyde dehydrogenase and as an alcohol deterrent, altering the intermediary metabolism of alcohol. This substance produces a sensitivity to alcohol, therefore when alcohol is ingested, blood acet-aldehyde concentrations are increased, leading to: flushing, systemic vasodilation, respiratory difficulties, nausea, hypotension, and other symptoms. Certain BED features resemble those of alcohol users, such as the urge to consume (food/alcohol) and the lack of control over their consumption.

**Anticonvulsants/Amines**

Antiepileptic agents, specifically topiramate, due to its modulatory effects on GABA<sub>α</sub> receptors (involved in calory intake) contribute to an improvement in eating behavior and weight loss. Sympathomimetic amine (in this case, the agent phentermine) is associated with a decrease in appetite reduction and food consumption – mostly for its action in releasing norepinephrine in the hypothalamus. The two are approved for obesity treatment by the FDA. The combination of both phentermine-topiramate involves the coadministration of drugs with opposing side-effect profiles. Phentermine stimulant-like properties may reduce topiramate sedative and cognitive side effects.

**Treatment Agents**

Table 1 summarizes all results.

**Dasotroline**

This drug is a dual dopamine and norepinephrine reuptake inhibitor and had been initially developed for attention deficit disorder (ADHD) treatment and Phase 3 trials had already been published. Its advantage, when compared to other stimulants or non-stimulant drugs used to treat ADHD, is its slow absorption rate and long elimination half-life which could diminish the potential for abuse and eliminate the problem of multiple dosing.

Three studies from the same pharmaceutic company, Sunovion, were performed for BED. The first one was a randomized 12-week treatment with placebo at a flexible dose (4, 6, 8 mg/day) with 317 patients. Significant reduction in binge eating was found starting from 6mg/d (−3.74 vs −2.75; P<0.0001) and the drug presented good tolerability after 1-year follow-up. The second study investigated the impact of dasotroline on weight in this very same cohort of patients in a 3-month trial. Weight changes were observed at week 12 for completers treated with dasotroline vs Placebo and evaluated by the body mass index (BMI) categories: normal weight (−4.6 vs −0.2), overweight (−5.8 vs +1.3), and combined obesity classes I–III (−6.2 vs +0.3).

In the third trial, a different sample of 486 participants with BED were selected and randomized to a placebo, dasotroline 4 mg/day, or dasotroline 6 mg/day. Dasotroline 6 mg/day, but not 4 mg/day, was superior to placebo for reducing binge eating episode days (−3.5 vs −2.9; P=0.004). Both doses produced significant reductions in obsessive-compulsive features of binge eating (P<0.001 and P<0.02) and global BED severity (P<0.01 and P<0.03). The drug was well tolerated in both studies, with the most common side effects being decreased appetite, dry mouth, anxiety, nausea, headache, constipation, and a modest increase in both pulse and blood pressure. On July 30, 2019, Sunovion announced the acceptance by the US FDA of the New Drug Application for dasotroline for the treatment of adults with moderate-to-severe BED. However, on May 13, 2020, Sunovion withdrew the application, citing that further clinical studies would be necessary to support regulatory approval. It should be noted that, previously, on August 31, 2018, the FDA had issued a letter determining that the drug could not be approved for the treatment of ADHD without additional data.

**Lisdexamfetamine**

Commercially known as Vyvanse, LDX was primarily developed as a treatment for ADHD tailored to increase attention span and decrease restlessness. This is an inactive prodrug derived from amphetamine by means of a unique mechanism involving an enzymatic process predominantly associated with the red blood cells. It was developed with the aim of providing a long-lasting and
consistent effect throughout the day along with reducing the potential for abuse.\textsuperscript{35}

Since 2015, a robust development program carried by the same research group composed by 3 short-term trials: one dose-finding Phase II study, two dose-optimization Phase III studies,\textsuperscript{36,37} and two long-term trials, were performed in order to investigate its safety and efficacy in BED treatment.\textsuperscript{38,39}

In the first study, a 11-week fixed-dose, parallel-group multicenter trial, with 259 adults across 30 sites in the USA diagnosed with BED and BMI between 25 and 40 kg/m, were randomized to receive LDX 30, 50, 70 mg/day or placebo. Seventy-eight percent of subjects completed the double-blind phase of the study. Binge eating episodes significantly decreased in the 50 and 70 mg/day treatment groups, but not in the 30 mg/day treatment group as compared to the placebo group. Specifically, in the LDX 50 mg/day group, binge days/week decreased from 4.5 to 0.4 ($P \leq 0.008$) and in the LDX 70 mg/day group binge days/week decreased from 4.6 to 0.5 ($P \leq 0.001$).\textsuperscript{36}

With the same participants sample, two subsequent trials used an enrichment strategy according to the following scheme: 1) 12-week open-label phase (dose optimization: 4 weeks of 50 or 70 mg); 2) dose maintenance of 8 weeks; 3) a 26-week, double-blind, randomized withdrawal phase; and 4) a follow-up visit. LDX was superior to placebo for reducing binge eating day frequency, global BED severity, and obsessive-compulsive features of binge eating. Significantly more LDX recipients had cessation of binge eating in both studies (36.2\% and 40\%) compared to placebo (13.1\% and 14.1\%, $p < 0.001$) and more significant body weight loss. In regards to the safety profile, adverse reaction rates beyond 50\% were not higher than those found with other psychotropic agents and were equally distributed across both active drug and placebo groups. In addition, both studies did not show elevated discontinuation rates due to adverse effects (6.3\% and 3.9\%). Also, although weight loss was not a primary endpoint, it was comparable to what have been found in trials with anti-obesity agents, ranging between 5 and 12 kg for the 12-week open-label phase. Finally, and not to be disregarded, there was some evidence that LDX has a low potential risk of abuse.\textsuperscript{36,37,40}

The randomized withdrawal maintenance of efficacy study\textsuperscript{36} examined rates of binge eating relapse in LDX treatment responders following 12 weeks of open-label treatment. The risk of binge eating relapse over a 6-month period was significantly lower in participants randomized to continuing LDX than in those randomized to placebo. The long-term safety and tolerability study consisted of a 1-year open-label extension trial of LDX in BED participants who had completed one of the three short-term trials. A mean (SD) of −7.04 (7.53) kg in weight reduction was reported at the end of the study.\textsuperscript{39}

LDX was the first medication to receive regulatory approval for the treatment of BED in the world (2015). It is specifically approved for moderate and severe BED in adults at 50–70 mg/day. The recommended starting dose in BED treatment is 30 mg/day with increments of 20 mg/day to achieve the recommended target dose of 50 to 70 mg/day.\textsuperscript{31}

**Methylphenidate**

Due to the strong association between dopamine and eating behavior, methylphenidate was selected to a randomized comparison with CBT in order to improve BED symptoms. Twenty two patients took a flexible-dosage ranging from 18 mg/d - 72 mg/d by the end of the fourth week and 27 patients completed the psychological treatment composed by 12 sessions. Both groups presented binge-free patients: 47\% for medication and 60\% for CBT, $\chi^2 = 0.62, p = 0.43$; subjective binge episode remission: 41\% for medication and 35\% for CBT, $\chi^2 = 0.15, p = 0.70$. As to weight loss, a significant difference in BMI was found at Week 12 compared to Week 0 for the methylphenidate group= 5.18, $p < 0.001$, but not for the CBT group= 1.54, $p = 0.13$. Despite the drug potential, the study hardly mentioned the side effects.\textsuperscript{41}

**Armodafinil**

A 10-week, randomized placebo-controlled trial was conducted with 30 BED patients for placebo and 30 BED patients for the armodafinil group (150–250 mg/d) neither with a current history of anorexia or bulimia nervosa. In the first analysis, there were no significant differences between the groups in reducing binge-eating day frequency. Armodafinil was associated to a greater reduction in binge eating frequency, BMI and obsessive symptoms.\textsuperscript{42}

**Oxytocin**

The effects of oxytocin on food intake, 24-h caloric consumption, salivary cortisol, and stress were measured in a randomized, placebo-controlled, crossover laboratory study in 25 women with BN or BED and 27 weight-matched women without a history of eating disorders.
Participants attended the lab for two experimental sessions, received a divided dose of 64IU of intranasal oxytocin in one session and an equivalent volume of a placebo nasal spray in the other. There were no significant effects of oxytocin on any measurements.\(^{24}\)

**Naltrexone Extended-Release + Bupropion ER**

Naltrexone extended-release + bupropion ER combination (NB) is an anti-obesity agent approved in the USA as an auxiliary component to dieting and physical activity for chronic weight management. Their combination was developed based on pre-clinical evidence that this association has complementary effects in the reduction of food intake. The first component is an opioid antagonist that has a high affinity for the \(\mu\)-opiod receptor which is related to eating behavior.\(^{43}\) The second one is an antidepressant (norepinephrine–dopamine reuptake inhibitor) that has shown efficacy in smoking remission and on weight loss. However, the use of bupropion alone did not improve binge eating behavior in a previous randomized trial.\(^{44}\) Interestingly, in a small retrospective cohort study, bupropion was effective in reducing binge frequency and, when compared to sertraline, achieved greater weight loss and improved sexual performance.

An open-label prospective study of 24 weeks was performed in 2017. The authors evaluated the NB combination therapy (32 mg/day of naltrexone ER and 360 mg/day bupropion ER) associated to diet and physical activity guidance in 25 overweight/obese subjects with depression. Medication was initiated at one-quarter of the daily maintenance dose and raised over the first 4 weeks of treatment. The binge eating scale (BES) scores were improved and maintained during the trial and, by week 8, there were no more patients that fulfilled the criteria for severe BDE. Overall, BDE symptoms and weight loss improved.\(^{45}\) An important limitation of the study was that 12 patients dropped out before week 24 (n=10 due to adverse events). Forty-eight percent of the patients considered these adverse effects moderate, mostly consisting of constipation (n = 8; 32%), headache (n = 8; 32%), insomnia (n = 8; 32%), dizziness (n = 7; 28%), and hot flushes (n = 7; 28%).

In 2020, a 16-week open label-trial, with 23 patients with obesity and BDE and a control group of 20 obese non-BED patients, was concluded. All patients should have undergone at least five weight-loss programs without success. NB of prolonged-release containing 8 mg of naltrexone and 90 mg of bupropion was initiated and slowly increased from 1 tablet a day up to a maximum of 2 tablets twice a day after the third week and followed by another 13 weeks maintenance phase. In parallel to NB, a 16-week lifestyle program, consisted of hypo-caloric diet, behavioral counseling and moderate aerobic physical activity was also implemented. Binge eating behavior weight loss improved in BDE patients (p=0.003). By the end of the treatment, achieved BMI was statistically similar between both groups (BED group = 35.8 ± 6.8 vs Control group = 40.3 ± 8.8; \(t = 1.687; p = 0.101\)).\(^{46}\)

**Vortioxetine**

The premise for vortioxetine use in BDE was based on the fact that a varied circuitries appear to be involved in BDE physiopathology.\(^{47,48}\) Thus, a multi-modal target medication, such as vortioxetine, could be helpful. Also, it appears to have a cognitive enhancing potential which may be useful in disorders that display an impaired executive control.\(^{49}\) For at least a year, eighty adults with BDE were recruited for a double-blind, placebo-controlled pilot study. Participants received a 12-week treatment with vortioxetine (10mg/day for the first week and subsequently 20mg/day) or placebo in a parallel design. Binge eating frequency was noted to be significantly reduced over time in both groups. Weight and BMI did not change over time (p>0.10). Thus, vortioxetine failed to be more effective than placebo for BDE treatment. (NCT02528409)

**Liraglutide**

GLP-1 was developed as a type 2 diabetes management; however, it is also used as an anti-obesity drug and sold in the form of a once-daily injection with effects known to inhibit appetite and delay gastric emptying in non-diabetic obese participants with BDE symptoms.

In a small randomized pilot study, 44 obese binge eaters were assigned to either a liraglutide 1.8mg + diet and exercise group or a control (diet + exercise) group for 12 weeks. Liraglutide participants showed significant reductions in BES [20 (IQR 18—27) to 11 (IQR 7—16), \(p < 0.001\)] and 81% (n=17/21) of them experienced a change in status from a binge eating to a non-binge eating category. Other measures were also improved such as body weight (94.54±18.14kg vs 90.14±19.70kg, \(p<0.001\)) and BMI (36.15 ± 3.84 kg/m\(^2\) to 34.40 ± 4.77 kg/m\(^2\), \(p<0.001\)). Nausea was the most prevalent adverse symptom.\(^{50}\)
In 2017, the binge eating liraglutide intervention study (BELIEVE) was initiated. A 17-week, randomized placebo-controlled trial tested the efficacy of liraglutide 3.0 mg/d compared to placebo in achieving remission of binge eating episodes and other clinical variables. The active comparator was a pre-filled, multi-dose pen that delivered doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg via subcutaneous injections. The medication was initiated at 0.6 mg daily for 1 week and then increased by 0.6 mg/day in weekly intervals until a dose of 3.0 mg/day was achieved. However, the study was terminated due to not meeting its recruitment goals. \(^{51}\) (NCT03279731)

### Disulfiram

In a 16-week study, doses of disulfiram 250mg/day were given to twelve obese patients with BED and without a history of alcoholism and heart disease. The agent significantly decreased the mean frequency of binge eating episodes per week from 7.9 ± 1.2 to 0.9 ± 0.6 (p b 0.001) and 7 participants (58.3%) achieved remission of binge eating. No changes in weight were observed and 11 participants presented important side effects. Additionally, three participants dropped out during the study, remaining a total of 9.\(^{52}\)

### Phentermine-Topiramate

Two previous open-label studies and one placebo-controlled trial had shown improvement in appetite and weight loss in obese BED patients.\(^{53}\) However, more controlled-trials aimed to establish optimal dosing and length of treatment were not performed. Also, cognitive impairment and somnolence were some of the most frequent adverse events that interfered with the patients' tolerability. The phentermine-topiramate (PHEN-TOP) combination was approved by FDA in 2012 for chronic weight management as an adjunct to a reduced-calorie diet and increased physical activity. The investigation of PHEN-TOP in BED treatment was based on a suggested evidence, in contrast to previous topiramate studies, that by lowering doses of topiramate in this combination it would be potentially effective in reducing binge eating behavior – thus being safer and more tolerable. The potential role for this drug association in BED treatment was that, in the present study, 18 participants with BED and 4 with BN over 18 years of age were enrolled in a flexible dosage (3.75mg/23mg-15mg/92mg) placebo-controlled crossover trial of 34 weeks. \(^{54}\)

### Agents’ Potential and Adverse Events

LDX, despite FDA approval for BED treatment, definitely presents some significant pros and cons; Table 1 shows details of every study efficacy. The amphetamine risk of abuse and dependence requires a careful evaluation before prescription. The safety profile is consistent with what was seen in studies using LDX in adults with ADHD; the most common adverse events in the adequate dose of 50–70 mg/d are: dry mouth (52%), decreased appetite (25%) and insomnia (19%) and 1.5% has serious adverse effects. The treatment group demonstrates efficacy compared to the placebo group in terms of decrease in BE days and cessation, and global improvement.\(^{36}\)

Overall, the second substance mostly investigated was dasotraline. Due to the smaller risk of abuse and dependence, compared to LDX, its development program was very encouraged, showing significant results with 6–8 mg/d on BE episodes vs placebo (−3.5 vs −2.9; P=0.0045). The most common adverse events on dasotraline were: insomnia, dry mouth, headache, decreased appetite, nausea, and anxiety.\(^{34}\) Despite the results, the laboratory withdraw the substance for BED treatment due to the need of further regulatory approval.

In the liraglutide study, forty-four obese BED participants were randomly assigned to intervention or control groups for 12 weeks. All participants received standard advice for diet and exercise. 81% (n=17/21) of those receiving liraglutide improved from binge eating to non-binge eating category, and 2 patients developed nausea. These results are still very scarce. In our opinion, sometimes the non-friendly presentation (injection pen) and the prevalence of nausea as the most common adverse effect are some weak points of the substance use.\(^{50}\)

The combination naltrexone-bupropion (already approved for obesity treatment in 2014), despite small groups of patients, was well succeed for diminishing BE severity and scores, as well as weight loss (8–9%). The most common side effects had very high rates: nausea (67%) and anxiety (22%), what may impair a sensitive group of patients to proceed. Another combination: phentermine-topiramate was evaluated in two small studies with favorable results, especially on weight loss (average of 6%). The most reported symptoms were: 52.4% (dry mouth), insomnia and paresthesia (28%).

Agents tested in few studies or small samples, such as armodafinil, oxytocin and vortioxetine despite being well tolerated, and presenting some impact of BE and weight,
did not present significant differences when compared to the control group. Findings in a methylphenidate and CBT study showed that both interventions were effective in BE measures, with a higher effect of the agent on weight loss (week 0 to week 12 = 5.18, p < 0.001).

**Innovative Treatments**

Some experimental drugs have been successfully tested in validated animal models of binge-like eating and could represent future investigations in clinical studies:

**CRF1 Receptor Antagonists**

Corticotropin releasing factor (CRF) represents a hormonal marker of BE induced by cyclic food restrictions and stress and may represent a novel pharmacological treatment for binge-related eating disorders. Indeed, systemic injections of R121919, but not of the metyrapone, were able to block binge-like eating behavior in female rats.\(^5\)

**Sigma-1 Receptor Antagonists**

Sig-1R system seems to contribute to the neurobiological adaptations driving compulsive-like eating, and thus pointing towards pharmacological treating of BED. The authors proved that the treatment with the selective Sig-1R antagonist BD-1063 dose-dependently decreased food responding in binge eating rats.\(^6\)

**Orexin-1 Receptor Antagonists**

Brain orexin 1 receptors (OX1Rs) are involved in food-motivated behavior. A study investigated the ability of OXR antagonist to block BE episodes and to evaluate the involvement of OX1 and OX2 mechanisms in the control of BE episodes in restricted and stressed animals. The results clearly indicate that the OX1R is involved in the control of BE episodes and suggested a potential role of OX1R antagonists to reverse BE episodes induced by stress and restricted diet.\(^7\) Other results with rats also suggest that hindbrain OX1Rs play a role in motivation for palatable food and that hindbrain OX1R stimulation can increase palatable, energy-dense food intake.\(^8\)

**Adenosine A2A Receptor Agonists**

Authors examined the effect of two A(2A) adenosine receptor (AR) agonists, CGS 21,680 and VT 7, on high-palatability food (HPF) intake in a model of BE in sated rats and on low-palatability food (LPF) intake in food-deprived rats. BE was induced in female rats by three 8-day cycles of food restriction/refeeding, followed by acute stress. The present study confirmed that the combination of stress and repeated episodes of food restriction is able to induce a pronounced binge eating response for HPF in rats.\(^9\)

**Discussion**

Since its categorization as an ED diagnosis in 2013, various studies have been published that investigated the effectiveness of different pharmacological treatments. Yet, up until now, the only drug approved by the FDA for BED treatment is LDX, which is not necessarily fit for all individuals with BED. Actually, in a real-life scenario, BED treatment could follow a variety of different algorithms and, in everyday practice, different off-label drugs are notably used as first-line agents.

Since 2015, only two antidepressant drug-trials have their efficacy in BED treatment investigated. In contrast to a previous study, which did not show improvement in binge eating behavior with bupropion treatment alone, NB treatment has been associated with BED improvement and some weight loss. According to previous evidence, it seems that for BED patients presenting with mood-related psychopathology, bupropion use might improve eating psychopathology as well. However, obese BED patients who did not present with clinically depressive symptoms would benefit more from NB treatment. Nevertheless, it should be noted that NB has been studied in small open-label trials and more extensive studies should still be performed. The second antidepressant investigated in BED treatment was vortioxetine. In spite of a lack of previous clinical evidence, findings showed that this drug has a limited efficacy of second-generation antidepressants when used alone in BED.

The next new promising agent, dasotraline, was chosen and is still expecting FDA approval. Overall, results from 2 double-blind studies, published by the same pharmaceutical industry, were favorable to its use in the reduction of BED episodes and reduction on obsessive traits related to eating behavior. In one of those investigations, dasotraline was also related to some modest weight loss. Nevertheless, the discontinuation of the dasotraline program diminished the chance to have a second FDA approved agent for the treatment of BED in the near future. In this regard, a similar discussion could be made in relation to the use of liraglutide for the treatment of BED. Though only a pilot open-label study has been demonstrated for its
benefits in reducing eating psychopathology in a small sample of obese patients – with high binge eating scale scores not formally diagnosed as BED and with an evident impact on weight reduction and safety profile – much expectation was given towards further studies. However, termination of its double-blind randomized trial also temporally puts away the chance of having liraglutide approved for BED. Of note, in clinical practice however, a significant percentage of patients that have been treated for obesity with liraglutide might have also been treated for BED, even if not clinically diagnosed, due to the higher prevalence of their comorbidity.

Considering the lack of evidence of armodafinil and oxytocin, the modest effect of disulfiram in an open trial and a favorable result of methylphenidate in a small randomized trial, the next drug awaiting for promising results in the treatment of BED might be the PHEN-TOP combination. Although only 2 small studies investigated its use for BED, some considerations might be worthy taking into account. Firstly, topiramate alone had previously showed to be effective in BED trials. Secondly, the premise to use a drug combination that allows smaller doses of topiramate to be tested increases its safety. Indeed, this can be evidenced in face of the PHEN-TOP approval for adjunct treatment of obesity in 2012. Lastly, the inclusion of patients with bulimia nervosa in one of the studies might shed some light on a future new drug for another ED.

The last 5 years have shown how difficult it is to prove sufficient efficacy and safety for new drugs in BED treatment. Since 2015, LDX has remained the only drug treatment option approved by the FDA. Interestingly, most studies of investigational drugs in this period were performed with agents that had already shown a positive impact on previous eating-related psychopathologies (though used in a different fashion as in naltrexone added on bupropion and phentermine added on topiramate) or had been known for its efficacy on obesity (liraglutide). However, much effort still needs to be employed as new studies are urgently needed – especially given the negative impact of BED on QL and clinical morbidity. Meanwhile, guidelines for BED treatment, particularly those targeting non-psychiatrists, should be considered towards a recommendation on the use of off-label agents and the need for individualizing drug treatment choices in accordance to clinical and psychiatric status.

Disclosure
Jose C Appolinario reports grants from Takeda Pharmaceutical, during the conduct of the study. The authors report no other potential conflicts of interest for this work.

References
1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth ed. Washington DC: American Psychiatric Association; 2013.
2. Kornstein SG, Kunovac JI, Herman BK, et al. Recognizing binge-eating disorder in the clinical setting: a review of the literature. Prim Care Companion CNS Disord. 2016;18(3). doi:10.4088/PCC.15r1905
3. Guerdjikova AI, McElroy SL, Winstanley EL, et al. Duloxetine in the treatment of binge eating disorder with depressive disorders: a placebo-controlled trial. Int J Eat Disord. 2012;45(2):281–289. doi:10.1002/eat.20946
4. Javara KN, Pope HG, Lalonde JK, et al. Co-occurrence of binge-eating disorder with psychiatric and medical disorders. J Clin Psychiatry. 2008;69(2):266–273. doi:10.4088/JCP.v69n0123
5. Friberg O, Martinussen M, Kaiser S, et al. Personality disorders in eating disorder not otherwise specified and binge eating disorder: a meta-analysis of comorbidity studies. J Nerv Ment Dis. 2014;202(2):119–125. doi:10.1097/NMD.0000000000000080
6. Kessler RC, Berglund PA, Chiu WT, et al. The prevalence and correlates of binge eating disorder in the World Health Organization World Mental Health Surveys. Biol Psychiatry. 2013;73:904–914. doi:10.1016/j.biopsycho.2012.11.020
7. Dingemans AE, van Furth EF. Binge eating disorder psychopathology in normal weight and obese individuals. Int J Eat Disord. 2012;45(1):135–138. doi:10.1002/eat.20905
8. Limna MS, Raevuori A, Haukka J, et al. Reproductive health outcomes in eating disorders. Int J Eat Disord. 2013;46(8):826–833. doi:10.1002/eat.22179
9. Raevuori A, Suokas J, Haukka J, et al. Highly increased risk of type 2 diabetes in patients with binge eating disorder and bulimia nervosa. Int J Eat Disord. 2015;48(6):555–562. doi:10.1002/eat.22334
10. Masheb RM, Grilo CM. Quality of life in patients with binge eating disorder. Eat Weight Disord. 2004;9(3):194–199. doi:10.1007/BF03325066
11. Vancampfort D, Probst M, Adriaens A, et al. Clinical correlates of global functioning in obese treatment seeking persons with binge eating disorder. Psychiatr Danub. 2014;26(3):256–260.
12. de Zwaan M, Herzpetz S, Zipfel S, et al. INTERBED: internet-based guided self-help for overweight and obese patients with full or sub-syndromal binge eating disorder. A multicenter randomized controlled trial. Trials. 2012;13(1):220. doi:10.1186/1745-6215-13-220
13. Wassenar E, Friedman J, Mehler PS. Medical complications of binge eating disorder. Psychiatr Clin North Am. 2019;42(2):275–286. doi:10.1016/j.psc.2019.01.010
14. Cossrow N, Pawaskar M, Witt EA, et al. Estimating the prevalence of binge eating disorder in a community sample from the United States: comparing DSM-IV-TR and DSM-5 criteria. J Clin Psychiatry. 2016;77(8):e968–e974. doi:10.4088/JCP.15m10059
15. Yager J, Devlin M, Halmi K, et al. Guideline Watch Practice Guideline for the Treatment of Patients with Eating Disorders. 3. Arlington, VA: American Psychiatric Assoc; 2012:1–18.
16. National Institute for Health and Care Excellence [NICE]; 2013. Available from: http://www.nice.org.uk. Accessed January 12, 2021.
17. Brownley KA, Berkman ND, Peat CM, et al. Binge-eating disorder in adults: a systematic review and meta-analysis. Ann Intern Med. 2016;165(6):409–420. doi:10.7326/M15-2455
Levitan; 41(5):1251–1260.
Kessler RM, Hutson PH, Herman BK, et al. The neurobiological basis of binge-eating disorder. *Neurosci Biobehav Rev.* 2016;63:223–238. doi:10.1016/j.neubiorev.2016.01.013

Kuikka JT, Tammela L, Karhunen L, et al. Reduced serotonin transporter binding in binge eating women. *Psychopharmacology (Berl.)* 2001;155(3):310–314. doi:10.1007/s002130010716

Gibb A, Deeks ED. Vortioxetine: first global approval. *Drugs.* 2014;74(1):135–145. doi:10.1007/s40265-013-0161-9

McElroy SL, Mori N, Guerdjikova AI, et al. Would glucagon-like peptide-1 receptor agonists have efficacy in binge eating disorder and bulimia nervosa? A review of the current literature. *Med Hypotheses.* 2018;111:90–93. doi:10.1016/j.mehy.2017.12.029

Culbert KM, Racine S, Klump KL. Hormonal factors and disturbances in eating disorders. *Curr Psychiatry Rep.* 2016;18(7). doi:10.1007/s11920-016-0701-6

Leisure M, Leppanen J, Paloyelis Y, et al. The influence of oxytocin on eating behaviours and stress in women with bulimia nervosa and binge eating disorder. *Mol Cell Endocrinol.* 2019;497:110354. doi:10.1016/j.mce.2018.12.014

Guerdjikova AI, Mori N, Casuto LS, McElroy SL. Novel pharmacologic treatment in acute binge eating disorder - role of lisdexamfetamine. *Neuropsychiatr Dis Treat.* 2016;12:833–841. doi:10.2147/NPT.S80881

Zhou FC, Lesch KP, Murphy DL. Serotonin uptake into dopamine neurons via dopamine transporters: a compensatory alternative. *Brain Res.* 2002;942:109–119. doi:10.1016/S0006-8993(02)02709-9

Valbrun LP, Zvonarev V. The opioid system and food intake: use of opiate antagonists in treatment of binge eating disorder and abnormal eating behavior. *J Clin Med Res.* 2020;12(2):41–63. doi:10.14740/jocmr4066

National Center for Biotechnology Information PubChem compound summary for CID 3117, disulfiram; 2020 Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Disulfiram. Accessed January 12, 2021.

Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology.* 2010;35:217–238. doi:10.1038/np.2009.110

Safer DL, Adler S, Dalai SS, et al. A randomized, placebo-controlled crossover trial of phentermine-topiramate ER in patients with binge-eating disorder and bulimia nervosa. *Int J Eat Disord.* 2020;53(2):266–277. doi:10.1002/eat.23192

Appolinario JC, Nardi AE, McElroy SL. Investigational drugs for the treatment of binge eating disorder (BED): an update. *Expert Opin Investig Drugs.* 2019;28(12):1081–1094. doi:10.1080/13543784.2019.1692813

Citrome L, Goldman R, Tsai J, et al. Dosartalone for treatment of adults with binge-eating disorder: effect on binge-related obsessions and compulsions. *CNS Spectr.* 2020;25(2):307–308.

Citrome L, Goldman R, Tsai J, et al. Effect of dosartalone on body weight in patients with binge-eating disorder. *CNS Spectr.* 2020;25(2):307.

Tsai J, Navia B, McElroy SL, et al. 170 efficacy and safety of dosartalone in adults with binge-eating disorder: a randomized, double-blind, fixed-dose trial. *CNS Spectr.* 2020;25(2):308–309. doi:10.1017/S1092852920000863

Goodman DW. Lisdexamfetamine dimesylate (vyvanse), a prodrug stimulant for attention-deficit/hyperactivity disorder. *P & T.* 2010;35(5):273–287.

McElroy SL, Hudson JI, Mitchell JE, et al. Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry.* 2015;72(3):235–246. doi:10.1001/jama psychiatry.2015.2162

McElroy SL, Hudson J, Ferreira-Cornwell MC, et al. Lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder: results of two pivotal phase 3 randomized controlled trials. *Neuropsychopharmacology.* 2016;41(5):1251–1260. doi:10.1038/npp.2015.275

Hudson NJ, McElroy SL, Ferreira-Cornwell MC, et al. Efficacy of lisdexamfetamine in adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry.* 2017;74(9):903–910. doi:10.1001/jamapsychiatry.2017.1889

Gasior M, Hudson J, Quintero J, et al. A phase 3, multicenter, open-label, 12-month extension safety and tolerability trial of lisdexamfetamine dimesylate in adults with binge eating disorder. *J Clin Psychopharmacol.* 2017;37(3):315–322. doi:10.1097/JCP.0000000000000702

Heal DJ, Smith SL, Gosden J, Nutt DJ. Amphetamine, past and present – a pharmacological and clinical perspective. *J Psychopharmacol.* 2013;27(6):479–496. doi:10.1177/0269881113482532

Quilty LC, Allen TA, Davis C, et al. A randomized comparison of long acting methylphenidate and cognitive behavioral therapy in the treatment of binge eating disorder. *Psychiatry Res.* 2019;273(273):467–474. doi:10.1016/j.psychres.2019.01.066

McElroy SL, Guerdjikova AI, Mori N, et al. Armadafinil in binge eating disorder: a randomized, placebo-controlled trial. *Int Clin Psychopharmacol.* 2015;30(4):209–215. doi:10.1097/YIC.0000000000000079

Greenway FL, Whitehouse MJ, Guttadauria M, et al. Rational design of a combination medication for the treatment of obesity. *Obesity.* 2009;17:30–39. doi:10.1038/oby.2008.461

White MA, McElroy CM. Buproprion for overweight women with binge-eating disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry.* 2013;74(4):400–406. doi:10.4088/JCP.12m08071

Guerdjikova AI, Walsh B, Shan K, et al. Concurrent improvement in both binge eating and depressive symptoms with naltrexone/bupropion therapy in overweight or obese subjects with major depressive disorder in an open-label, uncontrolled study. *Adv Ther.* 2017;34(10):2307–2315. doi:10.1007/s12325-017-0613-9

Carbone EA, Caroleo M, Rania M, et al. An open-label trial on the efficacy and tolerability of naltrexone/bupropion SR for treating altered eating behaviours and weight loss in binge eating disorder. *Eat Weight Disord.* 2020. doi:10.1007/s40519-020-00910-x

Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci.* 2010;13(5):635–641. doi:10.1038/nn.2519

Lagatiglia EC, Patrono E, Puglisi-Allegrac S, Ventura R. Food seeking in spite of harmful consequences is under prefrontal cortical noradrenergic control. *BMC Neurosci.* 2010;11:15. doi:10.1186/1471-2202-11-15

Mahableshwarkar AR, Jacobsen PL, Serenko M, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of vortioxetine in adults with major depressive disorder. *J Clin Psychiatry.* 2015;76(5):583–591. doi:10.4088/JCP.14m09337

Robert SA, Rohana AG, Shah SA, et al. Improvement in binge eating in non-diabetic obese individuals after 3 months of treatment with liraglutide - a pilot study. *Obes Res Clin Pract.* 2015;9(3):301–304. doi:10.1016/j.orcp.2015.03.005

Binge Eating Liraglutide Intervention (BELIEVE); 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT03279731?term=believe&draw=2&rank=3. Accessed January 12, 2021.

Farci AM, Piras S, Murgia M, et al. Disulfiram for binge eating disorder: an open trial. *Eat Behav.* 2015;16:84–87. doi:10.1016/j. eateh.2014.10.008

Tata AL, Kockler DR. Topiramate for binge-eating disorder associated with obesity. *Ann Pharmacother.* 2006;40(11):1993–1997. doi:10.1345/aph.1H178
54. Guerdjikova AI, Williams S, Blom TJ, Mori N, McElroy SL. Combination phentermine-topiramate extended release for the treatment of binge eating disorder: an open-label, prospective study. Innov Clin Neurosci. 2018;15(5–6):17–21.
55. Micioni Di Bonaventura MV, Lutz TA, Romano A, et al. Estrogenic suppression of binge-like eating elicited by cyclic food restriction and frustrative-nongrward stress in female rats. Int J Eat Disord. 2017;50(6):624–635. doi:10.1002/eat.22687
56. Cottone P, Wang X, Park JW, et al. Antagonism of sigma-1 receptors blocks compulsive-like eating. Neuropsychopharmacology. 2012;37(12):2593–2604. doi:10.1038/npp.2012.89
57. Piccoli L, Micioni Di Bonaventura MV, Cifani C, et al. Role of orexin-1 receptor mechanisms on compulsive food consumption in a model of binge eating in female rats. Neuropsychopharmacology. 2012;37(9):1999–2011. doi:10.1038/npp.2012.48
58. Kay K, Parise EM, Lilly N, et al. Hindbrain orexin 1 receptors influence palatable food intake, operant responding for food, and food-conditioned place preference in rats. Psychopharmacology (Berl). 2014;231(2):419–427. doi:10.1007/s00213-013-3248-9
59. Micioni Di Bonaventura MV, Cifani C, Lamberti C, et al. A2A adenosine receptor agonists reduce both high-palatability and low-palatability food intake in female rats. Behav Pharmacol. 2012;23(5–6):567–574. doi:10.1097/FBP.0b013e3283566a60