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REVIEW
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Anti-obesity Drugs for the Treatment of Binge Eating Disorder: Opportunities and Challenges

ABSTRACT

Binge eating disorder (BED) is the most prevalent form of disordered eating, frequently associated with obesity. Both these conditions along with sharing overeating behaviour features can lead to substantial burden of disease and premature mortality. With limited specific evidence available on pharmacotherapy, since lisdexamfetamine is approved only in some countries, new drugs are urgently needed to provide physicians with efficacious prescribing choices when treating BED. Although unique mechanisms underlie psychopathological features of binge eating, including impulsivity, compulsivity, and emotional reactivity, anti-obesity drugs might represent an option for both weight management and symptom reduction in people with BED. The aim of this review is thus to provide a summary of available evidence on the efficacy of anti-obesity drugs for BED. After comprehensively searching for relevant studies in PubMed and the Cochrane Library, as well as for unpublished results in ClinicalTrials.gov, we included 14 clinical trials. Despite the limited sample size and the methodological variability, evidence from available studies suggests that most anti-obesity drugs, namely phentermine/topiramate, naltrexone/bupropion, liraglutide and semaglutide, though not orlistat, might variously achieve improvements for both body weight and severity and frequency of binge episodes. Findings from ongoing clinical trials are likely to provide further insight into the possible role of anti-obesity drugs for treating BED. Since these agents can hold the potential to be misused potentiating dietary restriction and pathological weight loss, it is crucial to promote responsible prescribing practices.

Keywords: Anti-obesity agents, binge eating, eating disorders, obesity, weight loss

Introduction

Binge eating disorder (BED) is a psychiatric disorder characterized by recurrent binge eating (BE) in the absence of inappropriate compensatory behaviors aimed at preventing weight gain.[1] Binge eating disorder is the most prevalent eating disorder (ED), currently affecting 1.5% of women and 0.3% of men among the general population worldwide.[2] It can co-occur with depression, anxiety, substance use, borderline personality disorder, and cardiometabolic diseases, all of which contribute to a substantial burden of disease and premature mortality.[2] While none of the BED diagnostic criteria refers to weight, BED, though also involving normal-weight individuals, is more frequent in those with overweight and obesity (i.e., with a body mass index (BMI) ≥ 30 kg/m^2).[3,4] Indeed, among people seeking treatment for obesity, between 1.4% and 9% meet diagnostic criteria for BED[3] and recurrent BE episodes are found in up to 50% of those requiring bariatric surgery.[5] In addition, individuals with comorbid obesity and BED show significantly higher levels of general psychopathology in comparison to those without.[6] Binge eating disorder treatments are mainly aimed at enabling the patient to regain self-control, reducing the impulsive, compulsive, and perseverative drive to binge eat, thus decreasing the frequency and severity of BE episodes.[7] On the contrary, the key strategy for weight loss, i.e., dietary restriction, could even be considered detrimental for BED symptomatology, since susceptible individuals with comorbid EDs and obesity might not benefit from such lifestyle interventions due to their psychopathology.[8] Nevertheless, weight management should also be a primary relevant target, for its implications on general health and because obesity and resulting

Ilaria Riboldi[1]
Giuseppe Carrà[1,2]

[1]*School of Medicine and Surgery, University of Milano-Bicocca, Via Cadore, Monza, Italy*
[2]*Division of Psychiatry, University College London, Maple House, London, UK*

Corresponding author:
Ilaria Riboldi
✉ ilaria.riboldi@unimib.it

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body dissatisfaction are major triggers for BED symptoms.[9] Several psychological approaches, including cognitive behavioral therapy (CBT), interpersonal psychotherapy, dialectical behavioral therapy, and mindfulness training, have all demonstrated to reduce binge frequency, promoting abstinence, with benefits persisting for at least 1 year after treatment completion.[10,11] However, complementing approaches are likely to be needed for people whose EDs fail to respond satisfactorily to psychological interventions.[12] Randomized controlled trials (RCTs) involving different drugs, namely selective serotonin reuptake inhibitors, anticonvulsants, and norepineph rine/dopamine reuptake inhibitors, showed some improvement in BE behaviors, though less on body weight.[13,14] However, overall evidence on pharmacotherapy for EDs is limited compared to many other psychiatric disorders.[15] With lisdexamfetamine (LDX), a central nervous system stimulant, approved only in some countries for the treatment of moderate–severe BED,[16] new drugs are urgently needed to provide physicians with efficacious prescribing choices when treating BED.[15]

Given the recurrent overlap between BE and obesity, probably due to some shared features of overeating behaviors, the emerging literature for BED treatment has been influenced by matching research on obesity.[17] Therefore, some early interventions for BED management may include multiple behavioral weight-loss methods, as well as anti-obesity drugs.[3] These agents target peripheral and central pathways to decrease energy intake by reducing appetite and increasing satiety, while none of them has a direct effect on metabolism.[18] For example, among the most recent drugs studied as involved in weight control, the glucagon-like peptide 1 (GLP-1) agonists have been notably identified as drivers in conveying meal-related information of hunger and/or satiety to the brain, thus ideally playing a key role in BED treatment.[19] Although the anti-obesity drugs tested to date have shown some potential to boost weight loss in people with BED,[20] the efficacy on BE episodes and overall psychopathology is less clear.[20,21] One possible explanation is that BED may be associated with a distinct phenotype of obesity because of its unique neurobiological characteristics, leading to a peculiar perceived loss-of-control.[22] As compared to standard obesity, it may be linked to greater impulsivity and compulsivity, likely involving the meso-cortico-limbic dopamine system, thus requiring therapeutic agents that influence both reward and executive function systems.[21,22]

MAIN POINTS

- *With lisdexamfetamine approved only in some countries, additional drugs are needed for the treatment of binge eating disorder (BED).*
- *Anti-obesity drugs could be a treatment option based on features shared regarding overeating behaviors and the need for weight loss in people with BED.*
- *Despite several limitations, promising evidence on the efficacy of most anti-obesity drugs for weight loss and symptom reduction in BED is available.*
- *A better understanding of shared and distinct features characterizing BED and obesity will likely lead to a more focused use of anti-obesity drugs for BED.*
- *It is essential to raise awareness about potential risks and misuse of anti-obesity drugs in clinical and non-clinical populations.*

In this narrative review, we thus summarized the available evidence on anti-obesity drugs for BED, underlining their potential effects on BED specific mechanisms, along with relevant opportunities and challenges of their use in clinical practice.

Anti-Obesity Drugs

Six anti-obesity drugs, or combinations of them, are currently approved in the United States (US) and/or in European Union (EU) member states for the treatment of obesity. While orlistat, naltrexone/bupropion (N/B), liraglutide, semaglutide, and setmelanotide are approved in both the US and the EU, phentermine/topiramate (P/T) is licensed to treat obesity in the US but not in the EU. Tirzepatide, a gastric inhibitory polypeptide (GIP/GLP-1) dual agonist, was the last compound approved by the Food and Drug Administration (FDA) and the European Medicines Agency in November 2023.[23,24] Relevant characteristics of each anti-obesity drug, including the year of approval, mechanism of action, specific clinical warnings, and adverse effects, are reported in Table 1.

Methods

This review was conducted following the Scale for the Assessment of Narrative Review Articles items.[25] Only clinical studies testing the efficacy of approved anti-obesity drugs in individuals suffering from BED according to DSM-IV or DSM-5 criteria or positively assessed for BE behaviors through a validated tool were included. We excluded trials on withdrawn drugs, as well as clinical studies providing incomplete data. We searched PubMed and the Cochrane Library for trials published up to November 2023. ClinicalTrials.gov was searched for clinical trials completed, though yet unpublished, with reported findings. Our search strategy combined the following terms: "binge eating" AND "((anti-obesity drugs OR orlistat OR (phentermine AND topiramate) OR (naltrexone AND bupropion) OR liraglutide OR semaglutide OR setmelanotide OR tirzepatide))."

Results

Study Selection

Our searches generated 186, 60, and 20 trials from PubMed, the Cochrane Library, and ClinicalTrials.gov, respectively. We identified 14 eligible studies, i.e., 3 trials exploring the effects of orlistat;[26-28] 2 studies testing phentermine/topiramate;[29,30] 5 published,[31-35] and 1 unpublished studies[36] investigating naltrexone/bupropion; and 2 trials exploring liraglutide.[37,38] Moreover, an open-label retrospective cohort study testing semaglutide for individuals suffering from BED was included.[39] No clinical trial investigating setmelanotide nor tirzepatide in subjects with BED was identified. Main characteristics of included studies are shown in Table 2.

Outcome Measures

Despite some heterogeneity, changes in body weight and in BE psychopathology were the main outcomes evaluated by clinical trials included in this review. Weight loss was usually assessed as an overall BMI variation, as well as through the investigation of body composition (i.e., waist circumference, hip circumference, waist-to-hip ratio, body fat) and metabolic parameters (i.e., blood pressure, glucose, insulin, leptin, blood lipids). Binge eating disorder psychopathology was evaluated using a number of different assessment tools (see Table 2 for a comprehensive list). In addition, both the frequency and

Table 1. Characteristics of Anti-Obesity Drugs Based on Relevant Technical Reports

Drug Country: Year of Approval	Mechanism of Action	Specific Clinical Warnings[a,b]	Adverse Events[b,c]
Orlistat • **United States: 1999** • **European countries: 1998**	**Gastric and pancreatic lipase inhibitor**	• Patients with chronic malabsorption syndrome or cholestasis • Pregnancy	- Abdominal distress/pain - Steatorrhea
Phentermine/topiramate • **United States: 2012** • **European countries: currently not approved**	**NE receptor agonist/GABA receptor agonist, glutamate receptor antagonist**	• Patients with chronic malabsorption syndrome or cholestasis • Glaucoma • Hyperthyroidism • Concomitant use of MAOIs • Hypersensitivity to sympathomimetic amines • Pregnancy	- Elevation in heart rate - Mood and sleep disorders - Cognitive impairment - Metabolic acidosis - Paresthesia - Dry mouth - Paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth
Naltrexone/bupropion • **United States: 2014** • **European countries: 2015**	**Opioid receptor antagonist/DA, NE reuptake inhibitor**	• Chronic opioid use • Acute opioid withdrawal • Uncontrolled hypertension • Seizure disorder • Bulimia or anorexia nervosa • Abrupt discontinuation of alcohol/benzodiazepines/antiseizure drugs • Concomitant use of MAOIs • Pregnancy	- Nausea - Constipation - Headache - Vomiting - Dizziness - Insomnia - Dry mouth - Diarrhea - Sleep disorder
Liraglutide • **United States: 2014** • **European countries: 2015**	**GLP-1 analogue**	• Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 • Pregnancy	- Increased heart rate - Hypoglycemia - Constipation - Diarrhea - Nausea - Vomiting - Headache
Semaglutide • **United States: 2021** • **European countries: 2021**	**GLP-1 analogue**	• Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 • Pregnancy	- Nausea - Vomiting - Diarrhea - Abdominal pain - Constipation - Headache
Setmelanotide • **United States: 2020** • **European countries: 2021**	**MC4R agonist**	• None	- Injection site reactions - Hyperpigmentation - Nausea - Headache - Diarrhea - Vomiting - Abdominal pain
Tirzepatide • **United States: 2023** • **European countries: 2023**	**GIP/GLP-1 dual agonist**	• Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 • Known serious hypersensitivity to tirzepatide or any of the excipients	- Nausea - Diarrhea - Decreased appetite - Vomiting - Constipation - Dyspepsia - Abdominal pain

DA, dopamine; FDA, Food and Drug Administration; GABA, gamma-aminobutyric acid; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; IV, intravenous; MAOIs, monoamine oxidase inhibitors; MC4R, melanocortin-4 receptor; NE, norepinephrine.
[a]Specific clinical warnings were based on the FDA approval leaflet.
[b]Chakhtoura M, Haber R, Ghezzawi, et al. Pharmacotherapy of obesity: an update on the available medications and drugs under investigation. *EClinicalMedicine*. 2023;58:101882.[18]
[c]Adverse events were based on the FDA approval leaflet.

severity of subjective and objective binge episodes,[40] along with specific features of dietary restraint, i.e., rigid (defined by dichotomous, all-or-nothing approaches to dieting) and flexible (reflecting a moderated approach to dieting) attitudes,[41] were included in some trials for the evaluation of BED.

Orlistat and Binge Eating Disorder

Data from 3 clinical trials testing the effect of orlistat on BED were available (Table 2). The first study was published in 2005[26] and evaluated whether medication with orlistat could reduce body weight and binge frequency in 89 obese subjects suffering from

Table 2. Characteristics of the Included Studies

Study	Intervention	Study Design	Participants	Main Outcomes (Changes In)	Effects on Body Weight and BED
			Orlistat		
Golay A. et al, 2005	Orlistat (120 mg/day)	24-week randomized, double-blind, placebo-controlled trial	89 obese subjects with BED	• Body weight, body composition and metabolic parameters; • Binge eating (EDI).	• Subjects receiving orlistat lost significantly more weight (−7.4%) than placebo (−2.3%) ($P = .0001$). • EDI score was significantly lower in the orlistat group (48.7 vs. 58.5; $P = .011$). • No significant difference in the percentage of subjects still classified as binge eaters (orlistat = 23%; placebo = 29%) ($P = .539$).
Grilo C. M. et al, 2005	Orlistat (120 mg/day) + cognitive behavioral therapy (CBT)	12-week randomized, double-blind, placebo-controlled trial	50 obese subjects with BED	• Body weight; • Binge eating (EDE); • Cognitive restraint (EDE-Q, TFEQ).	• Participants receiving orlistat + CBT were significantly more likely to achieve a 5% weight loss at both post-treatment (36% vs. 8%) and 3-month follow-up (32% vs. 8%). • Participants receiving orlistat + CBT were significantly more likely to report binge abstinence at post-treatment (64% vs. 36%; n = 16 vs. n = 9) but not at 3-month follow-up (both 52% abstinence rates). • The treatment groups did not differ significantly on any of the restraint measures.
Grilo C. M. et al, 2013	Orlistat (120 mg/day) + behavioral weight loss treatment (BWL)	4-month randomized, double-blind, placebo-controlled trial	79 obese subjects with BED (n = 40) and without BED (n = 39)	• Body weight; • Binge eating (EDE).	• Orlistat produced significant weight loss in obese subjects without BED, but not in those with BED. • BED remission rates: orlistat + BWL = 60% vs. placebo + BWL = 70%, showing no additional improvement from the orlistat intervention ($P = .51$).
			Phentermine/Topiramate		
Guerdjikova A. I. et al, 2018	Phentermine (7.5 mg/day) + topiramate (46 mg/day)	12-week open-label, prospective trial	10 obese subjects with BED	• Body weight, metabolic parameters; • Binge eating (EDE-Q, BES).	• Minimal weight loss in the majority of participants, weight-loss >5% in 20% of subjects only. • Significant reduction in binge episodes/week ($P < .01$), BES score ($P < .01$), and EDE-Q weight ($P = .02$) and shape ($P = .03$) concern subscale score at endpoint.
Safer D. L. et al, 2020	Phentermine (3.75-15 mg/day) + topiramate (23-92 mg/day)	34-weeks randomized, double-blind placebo-controlled, crossover trial	22 subjects with BED (n = 18) or BN (n = 4) (Normal weight = 3 (13.6%); Overweight = 7 (31.8%); Obese = 12 (54.5%))	• Body weight; • Number of OBE days over the last 4 weeks, SBE days, SBE episodes, and abstinence over prior 28 days (EDE); • Subscales for dietary restraint, eating concerns, shape concerns, weight concerns, and global subscale score (EDE-Q); • Subscales for cognitive restraint, disinhibition, and perceived hunger (TFEQ); • Binge eating severity (BES).	• Weight loss for participants on P/T was 6.4% (range: −1.1 to −13.3%). When crossed over to placebo, they regained weight on average about 1.5%. When examining weight loss by diagnosis, BED patients lost an average of 6.2 kg (SD 3.7). • P/T significantly reduced OBE days by 7.3 days compared to placebo (95% CI −10.4 to −4.2; effect size = 0.93) ($P < .0001$). • Abstinence from OBEs in 63.6% of participants while on P/T compared to 9.1% on placebo ($P < .0001$. • Other secondary outcomes showing a statistically significant improvement with P/T were OBE episodes ($P = .002$), total OBE + SBE episodes ($P < .0001$), the EDE-Q global score ($P = .007$), as well as eating concern ($P < .0001$) and shape concern ($P = .007$) subscales, and the TFEQ hunger subscale ($P = .003$).

(*Continued*)

Table 2. Characteristics of the Included Studies (Continued)

Study	Intervention	Study Design	Participants	Main Outcomes (Changes In)	Effects on Body Weight and BED
			Naltrexone/Bupropion		
Guerdjikova A. I. et al, 2017	Naltrexone (32 mg/day) + bupropion (360 mg/day)	24-week open-label, single-arm trial	25 obese women with comorbid MDD, 91% with moderate/severe BE	• Body weight; • Binge eating severity (BES); • Difficulty in controlling eating (CoEQ).	• Significant, substantial weight loss (−9.2% [8.9 kg] from baseline) ($P < .001$). • BES scores were significantly improved at the first post-baseline measurement and improvement was maintained throughout the trial. • N/B was associated with significant reductions in CoEQ score ($P < .001$).
Carbone E. A. et al, 2021	Naltrexone (32 mg/day) + bupropion (360 mg/day)	16-week open-label trial	43 obese subjects with BED (n = 23) and without BED (n = 20)	• Body weight; • Binge eating, eating restraint, eating concern, weight concern, and shape concern (EDE-Q); • Binge eating severity (BES); • Addiction-like eating behaviour (YFAS).	• Significant weight loss with high effect size ($\eta^2 > 0.8$) regardless diagnosis. • Among BED patients, EDE-Q eating restraint significantly increased ($P = .031$; $\eta^2 = 0.16$), EDE-Q weight concern decreased ($P = 0.048$; $\eta^2 = 0.13$). BES score ($P = .04$; $\eta^2 = 0.13$), as well as the severity of food addiction by YFAS ($P = .003$; $\eta^2 = 0.14$) significantly decreased. Total number of DSM-5 criteria for BED significantly decreased ($P = .03$; $\eta^2 = 0.14$). • Among BED patients, significant reductions in binge ($P = .003$), grazing ($P = .013$), craving for carbohydrates ($P = .001$), emotional eating ($P = .021$), and post-dinner eating ($P = .021$) were measured. • No effect on EDE-Q total score ($P = .9$).
Grilo C. M. et al, 2021	Naltrexone (50 mg/day) + bupropion (300 mg/day)	12-weeks randomized, double-blind, placebo-controlled trial	22 obese subjects with BED	• Body weight; • Binge eating frequency and eating-disorder; • BED psychopathology (EDE, EDE-Q).	• The percentage of patients who attained 3% weight loss was significantly greater with N/B than with placebo (45.5% vs. 0%). • No significant reductions in binge-eating or general eating psychopathology between N/B and placebo.
Grilo C. M. et al, 2022	• Naltrexone (32 mg/day) + bupropion (360 mg/day) • Naltrexone (32 mg/day) + bupropion (360 mg/day) + behavioural weight loss treatment (BWL)	16-weeks randomized, double-blind, placebo-controlled trial	136 obese subjects with BED	• Body weight, metabolic parameters; • Binge eating frequency; • BED psychopathology (EDE, EDE-Q); • Subscales for cognitive restraint, disinhibition, and perceived hunger (TFEQ); • Food craving (FCI); • Psychological drive to consume palatable foods (PFS).	• Weight loss did not differ significantly between the N/B and placebo. • Binge eating remission rates: 31.3% (N/B), 17.7% (placebo), 57.1% (N/B+BWL), 37.1% (placebo+BWL). N/B was significantly superior to placebo. • Analyses of secondary measures of eating disorder did not reveal significant reductions and improvements for N/B.
Grilo C. M. et al, 2023	Naltrexone (32 mg/day) + bupropion (360 mg/day)	12-weeks randomized, double-blind, placebo-controlled trial	89 subjects with BED, 77.5% BMI ≥ 30 kg/m^2	• Body weight, metabolic parameters; • Binge eating frequency; • BED psychopathology (EDE); • Subscales for cognitive restraint, disinhibition, and perceived hunger (TFEQ); • Food craving (FCI); • Psychological drive to consume palatable foods (PFS).	• N/B was associated with significantly greater weight loss than placebo (≥5% weight loss than placebo (27.9% vs. 6.5%; $P = .001$). • Binge-eating frequency revealed substantial reductions that did not differ significantly between the N/B and placebo ($P = .83$). • Binge-eating remission rates revealed that N/B and placebo did not differ significantly ($P = .43$).

(*Continued*)

Table 2. Characteristics of the Included Studies (Continued)

Study	Intervention	Study Design	Participants	Main Outcomes (Changes In)	Effects on Body Weight and BED
NCT03047005, 2023	Naltrexone (32 mg/day) + bupropion (360 mg/day)	16-week randomized, double-blind, placebo-controlled trial	68 obese subjects with BED	• Body weight; • Binge eating frequency.	• Patients who received N/B obtained an average weight loss of −0.03 (SD 0.05) compared to placebo 0.01 (SD 0.04). • In patients who received N/B, the number of binge days in a month was 0.86 (SD 2.15), in those who received placebo 3.25 (SD 7.06).
Liraglutide					
Robert S. A. et al, 2015	Liraglutide (1.8 mg/day) subcutaneous injection	12-week randomized, prospective, controlled trial	44 obese subjects with BE	• Body weight, anthropometric parameters (ghrelin levels); • Binge eating (BES).	• Participants who received liraglutide had significant reductions in body weight ($P < .001$), BMI ($P < .001$), waist circumference ($P = .004$), systolic blood pressure ($P = .042$), fasting glucose ($P = .027$), and total cholesterol ($P = .044$) compared to the control group (diet and exercise). • Participants who received liraglutide had significant reductions in BES ($P < .001$).
Allison K. C. et al, 2023	Liraglutide (3 mg/day) subcutaneous injection	17-week pilot double-blind, randomized, placebo-controlled trial	27 obese subjects with BED	• Body weight; • Binge eating frequency (EDE); • Cognitive estraint, disinhibition, and hunger (EI).	• At week 17, the liraglutide group had a significantly larger mean weight loss of 4.7 kg (95% CI 2.9, 6.4), compared to the 0.9 kg loss (95% CI −0.6, 2.5) of the placebo group ($P = .003$). • Binge episode frequency declined by a mean of 4.0 (SD 0.6) episodes per week in the liraglutide group. No significant difference with placebo ($P = .37$). • No difference in binge-eating remission rate (44% vs. 36%) defined as reporting no OBEs within the prior 2 weeks ($P = .76$). • No difference in changes in eating behavior disinhibition ($P = .25$), cognitive restraint ($P = .38$), or hunger ($P = .58$) between the groups.
Semaglutide					
Richards J. et al, 2023	• Semaglutide (SEMA) SC • Alternative anti-obesity medications (AOM) but not semaglutide • Semaglutide + topiramate or LDX (SEMA+AOM)	Open-label, retrospective cohort study	48 obese subjects with BED	• Binge eating (BES).	• Significant difference in the mean change in BES score between the SEMA group and the AOM group ($P < .01$), as well as between the SEMA group and the SEMA+AOM group ($P < .01$). • Findings were similar in patients with moderate/severe BED, as well as the full sample.

BED, binge eating disorder; BE, binge eating; BES, Binge Eating Scale[46]; CoEQ, Control of Eating Questionnaire[64]; EDI, Eating Disorder Inventory[42]; EDE, Eating Disorder Examination interview;[45] EDE-Q, Eating Disorder Examination Questionnaire;[43] EI, Eating Inventory;[67] FCI, Food Craving Inventory;[65] LDX, lisdexamfetamine; PFS, Power of Food Scale[66] OBE, objective binge eating; N/B, naltrexone/bupropion; P/T, phentermine/topiramate; SBE, subjective binge eating; SC, subcutaneous injection; TFEQ, Three Factor Eating Questionnaire;[44] YFAS, Yale Food Addiction Scale.[47]

BED. Using a double-blind design, orlistat 120 mg/day or placebo was administered for 24 weeks. Body weight, anthropometric parameters, as well as BE psychopathology by the Eating Disorder Inventory (EDI)[42] were assessed. Authors found that the anti-obesity drug induced weight loss in obese individuals with BED ($P = .0001$), though without any significant difference as for the proportion of subjects remaining classifiable as binge eaters (orlistat = 23%; placebo = 29%) ($P = .539$), despite lower scores at EDI in the orlistat group ($P = .01$).

In another study, Grilo and colleagues[27] examined changes in dietary restraint in 50 obese individuals suffering from BED and receiving CBT combined with either orlistat or placebo. Participants from the CBT + orlistat group were significantly more likely—compared to placebo (64% vs. 36%)—to achieve a 5% weight loss at both post-treatment and 3-month follow-up, and to report binge abstinence post treatment. However, abstinence was not maintained at follow-up, and the treatment group did not significantly differ on any of the dietary restraint measures assessed by both the Eating Disorder

Examination Questionnaire (EDE-Q)[43] and the Three Factor Eating Questionnaire.[44]

The limited effect of orlistat on BED was confirmed by a subsequent double-blind RCT conducted in 2013.[28] Seventy-nine subjects were randomly assigned to a 4-month orlistat course plus a behavioral weight loss (BWL) program or to placebo plus BWL. The authors found that BED remission rates, measured using the Eating Disorder Examination (EDE) interview,[45] were similar for the placebo/BWL group and the orlistat/BWL group (70% vs. 60%). Orlistat significantly reduced weight only in obese subjects without BED, suggesting that this disorder substantially impaired its effect on weight loss.

Phentermine/Topiramate and Binge Eating Disorder

Two clinical trials tested the association of phentermine and topiramate on individuals suffering from BED. Details are shown in Table 2.

The first clinical trial, published in 2018,[29] tested changes in body weight as well as in BE frequency, severity, and psychopathology as assessed by the Binge Eating Scale (BES)[46] and EDE-Q, in individuals receiving phentermine + topiramate (7.5 mg/day, 46 mg/day). In this open-label, uncontrolled trial, while authors uncovered minimal weight loss in the vast majority of the sample, a significant reduction in binge episodes per week, along with BES and EDE-Q weight and shape concern subscale scores, was found ($P < .05$).

Another clinical trial based on 22 obese individuals (18 suffering from BED and 4 from bulimia nervosa) showed positive results on the primary outcome, i.e., weight change from baseline.[30] Indeed, the average weight loss for subjects with BE who were on phentermine/topiramate was 6.2 kg (SD 3.7). When subjects crossed over to placebo, they regained average of 1.5% of their lost weight. In addition, P/T reduced the number of days over the last 4 weeks characterized by objective BE by 7.3 days ($P < .0001$). Abstinence from objective BE episodes was reported by 63.6% of participants while on the anti-obesity drug compared to 9.1% when on placebo ($P < .0001$).

Naltrexone/Bupropion and Binge Eating Disorder

Five published and 1 unpublished (with results available on ClinicalTrials.gov as accessed on 15 December 2023) studies reported on 6 clinical trials testing the association of naltrexone/bupropion for BED (Table 2).

Guerdjikova AI et al[31] conducted a 24-week open-label, single-arm trial in 2017, investigating the effects of N/B in terms of changes in both self-reported BE behavior and body weight. Twenty-five obese women with comorbid major depressive disorder and BE were administered naltrexone (32 mg/day) and bupropion (360 mg/day), resulting in significant weight loss, along with a significant reduction in BES scores and in difficulties in controlling eating ($P < .001$).

In a more recent open-label, uncontrolled trial,[32] the authors evaluated the effects of naltrexone (32 mg/day) and bupropion (360 mg/day) on weight loss, BE behavior, and psychopathology assessed by EDE-Q, BES, and the Yale Food Addiction Scale (YFAS),[47] among 43 obese subjects with (n = 23) and without (n = 20) BED. Among individuals suffering from BED, improvements in eating psychopathology were shown through a significant increase in EDE-Q flexible restraint ($P = .031$), as well as a decrease in EDE-Q weight concern scores ($P = .048$). Moreover, pathological eating behavior (i.e., binge, grazing, emotional eating, craving for carbohydrates, and post-dinner eating), BES score ($P = .04$), and YFAS severity ($P = .003$) all significantly improved. Despite no effects on EDE-Q total score, significant weight loss was measured regardless of BED diagnosis.

However, subsequent double-blind placebo-controlled RCTs found mixed findings for this anti-obesity agent. More in detail, in 22 obese subjects with BED enrolled by Grilo and colleagues,[33] the allocation to naltrexone (50 mg/day) + bupropion (300 mg/day) provided changes in body weight significantly larger than placebo, while reductions in BE and eating-disorder psychopathology did not differ significantly between the N/B and placebo subgroups. In addition, in an RCT published in 2022,[34] it was tested the efficacy of naltrexone/bupropion and BWL therapy, alone and combined, was tested for BED comorbid with obesity. Even if BE remission rates demonstrated that N/B was significantly superior to placebo (17.7% for placebo, 31.3% for N/B, 37.1% for placebo + BWL, and 57.1% for N/B + BWL), analyses of secondary measures of ED psychopathology as well as of weight loss did not reveal significant improvements attributable to naltrexone/bupropion.

Moreover, naltrexone/bupropion was associated with significantly greater weight loss than placebo in 89 obese subjects with BED.[35] Otherwise, in the same sample, BE frequency ($P = .83$) and remission rates ($P = .43$) had reductions that did not significantly differ between N/B and placebo subgroups.

Finally, 1 RCT testing naltrexone/bupropion[36] was registered on ClinicalTrials.gov. Its aim was to examine the efficacy of this anti-obesity agent as a maintenance therapy for the treatment of BED in patients with obesity. Among subjects who received naltrexone/bupropion, the number of BE days in a month was lower compared to those who were allocated to placebo [0.86 (SD 2.15) vs. 3.25 (SD 7.06)]. In addition, the N/B group showed an average weight variation of −0.03 (SD 0.05), compared to placebo [0.01 (SD 0.04)].

Liraglutide and Binge Eating Disorder

Data from 2 clinical trials testing the effects of liraglutide on BE were available (Table 2). The first study was published in 2015.[37] Participants who received 1.8 mg/day of liraglutide had significant reductions both in body weight ($P < .001$) and in BES scores ($P < .001$), as compared with a control group receiving just diet and exercise. Furthermore, in a 17-week double-blind placebo RCT, Allison and colleagues enrolled 27 obese subjects with BED.[38] At the end point, the liraglutide group had a significantly larger mean weight loss of 4.7 kg (95% CI 2.9, 6.4), compared to the 0.9 kg loss (95% CI −0.6, 2.5) of placebo-treated participants. Nevertheless, binge episode frequency declined by a mean of 4.0 (SD 0.6) episodes per week in the liraglutide group, which did not significantly differ from the placebo group ($P = .37$).

Semaglutide and Binge Eating Disorder

So far, only 1 study tested the efficacy of semaglutide on eating psychopathology in obese subjects suffering from BED (Table 2). This open-label retrospective cohort study[39] examined the effects of semaglutide on BES scores in a sample of 48 individuals. Participants were divided into 3 groups: those prescribed semaglutide, those prescribed either LDX or topiramate, and those prescribed a combination of semaglutide with LDX or topiramate. Interestingly, subjects with both moderate and severe BED from the semaglutide-only

group showed greater reductions in BES scores compared to the others group ($P < .01$).

Other Anti-obesity Drugs

Setmelanotide is a melanocortin 4 (MC4) receptor agonist that was approved by the FDA in 2020 as a subcutaneous injectable formulation for chronic weight management in subjects suffering from rare obesity syndromes.[18] Tirzepatide is a gastric inhibitory polypeptide GIP/GLP-1 dual agonist that works centrally to decrease food intake and possibly increase energy expenditure by desensitizing the GIP receptor in preclinical models.[18] Despite their availability, no study has tested these 2 anti-obesity drugs for the treatment of BED symptoms so far.

Discussion

This comprehensive review synthesized the main findings from available research on the treatment of BED with anti-obesity drugs. We reported evidence from clinical studies analyzing the potential effects of these agents on both weight loss and eating symptomatology in obese subjects suffering from BED. Several meaningful findings deserve consideration. First, available evidence seems to indicate that anti-obesity drugs, namely phentermine/topiramate, naltrexone/bupropion, and liraglutide, though not orlistat, might variously achieve improvements in both body weight and the severity and frequency of binge episodes. Moreover, the effect of semaglutide on eating symptoms, but not on weight management, in individuals suffering from BED has been preliminarily tested, showing promising results. However, additional research is needed, considering the limited sample size of the involved studies, their methodological variability, and the inconsistency of findings, which did not allow us to draw firm conclusions.

More in detail, RCTs testing orlistat for BED showed mixed results on the reduction of body weight, but no significant differences between active treatment and placebo on general BED psychopathology.[26-28] Conversely, both an uncontrolled trial and an RCT showed the efficacy of P/T on BED severity and BE frequency, along with significant variations in body weight.[29,30] While in open-label, uncontrolled studies promising effects were found of N/B on both weight loss and BED severity,[31,32] mixed findings were uncovered in double-blind RCTs.[33-36] Based on the hypothesis that GLP-1 analogues might play a key role in brain hunger and/or satiety information,[19] few recent trials proved that these drugs could be useful in BED treatment. Indeed, liraglutide treatment was associated with significant reductions in body weight, as well as in BES scores in obese subjects with BE.[37] This effect on weight was recently confirmed, though BE frequency and overall symptoms did not achieve significant improvement.[38] Another GLP-1 analogue, semaglutide, has been tested only in a single retrospective open-label study, though suggesting promising effects for BED symptoms.[39]

Finally, the circumscribed clinical indications of setmelanotide, approved only for rare obesity syndromes,[18] is likely to explain the current lack of evidence for BED psychopathology. Similarly, tirzepatide has been only recently approved for the treatment of obesity.[18]

Despite little existing evidence on shared and distinct features characterizing BED and obesity, well-established pathophysiological mechanisms add neurobiological plausibility to the potential efficacy of anti-obesity drugs for BED, thus laying the foundations for future research. First, orlistat is a non-systemically acting weight management agent that promotes weight loss through the partial inhibition of dietary fat absorption.[26] Indeed, through the inactivation of gastric and pancreatic lipases, orlistat prevents the transformation of triglycerides into absorbable free fatty acids and monoglycerides.[26] It has been thus hypothesized that orlistat may be beneficial at least for weight loss in subjects with BED by disrupting a potential cycle of elevated dietary fat intake.[12,26]

Second, phentermine, a monoaminergic drug, along with its dose-related improvements in executive functioning, centrally reduces hunger by modulating catecholamine release, thus possibly contributing to controlling BE.[48,49] In addition, BED seems to be characterized by increased impulsivity, which results in good responsiveness to catecholaminergic drugs, thus probably explaining the efficacy of LDX as well as phentermine on eating symptomatology.[17]

Moreover, topiramate, a gamma-aminobutyric acid receptor agonist, glutamate receptor antagonist, and carbonic anhydrase inhibitor, has been shown to suppress appetite, although through mechanisms that are still unclear.[18,49,50] Despite animal studies showing that topiramate can lead to heightened energy expenditure and enhanced insulin sensitivity, alongside a reduction in food intake possibly due to its glutamate antagonism within the lateral hypothalamus, these effects have not been confirmed in humans yet.[18,50]

A key clinical rationale for exploring the utilization of a combination of phentermine and topiramate in individuals suffering from BED lies in the possibility of enhancing pharmacotherapy safety by exploiting their opposing side-effect profiles.[51] In addition, P/T may have synergistic effects, allowing for lower doses and greater efficacy of both drugs compared with monotherapy.[51]

As for the naltrexone/bupropion formulation, this includes an antiopioid agent and an antidepressant, working at the level of appetite/food intake regulation in conjunction with reward and executive function systems possibly involved in the pathogenesis and maintenance of BED symptoms.[52,53]

Also, GLP-1 analogues induce weight loss through multiple mechanisms, including insulin stimulation, inhibition of glucagon secretion, delaying gastric emptying, enhancing satiety, reducing hunger, and regulating appetite and food reward, thus potentially acting on BE behaviour.[19]

Finally, the highly prevalent comorbidity between substance use disorder (SUD) and EDs, possibly attributable to shared psychopathological and neurophysiological pathways, might explain the likely efficacy on BED symptoms of topiramate, naltrexone, and GLP-1 analogues, which have already shown at least partial effects in individuals with SUD.[54,55] Beyond SUD, the frequent co-occurrence of BED with depression, anxiety, as well as other psychiatric comorbidities, requires a cautious and tailored use of anti-obesity medications.[2]

Although findings from available clinical trials seem to support anti-obesity drugs as promising treatments for BED, additional studies are needed before claiming their efficacy and acceptability. For example, some ongoing trials registered in ClinicalTrials.gov, namely i) a 12-week study investigating the efficacy and effectiveness of

naltrexone/bupropion compared with placebo as a treatment for subjects not responding to acute treatments;[56] and ii) a retrospect ive/prospective cohort study testing the effect of semaglutide on body weight and BED symptomatology,[57] both likely to shed additional light on the efficacy of anti-obesity drugs for BED.

Clinical Opportunities and Challenges for the Use of Anti-Obesity Drugs for Binge Eating Disorder

The use of anti-obesity drugs for BED is supported to a certain extent by the findings of this review. Indeed, psychological and behavioral therapies, as well as the vast majority of other drugs tested for the treatment of BE symptoms, showed an unsatisfactory effect on the desirable weight loss, thus even more encouraging the use of anti-obesity agents for people with BED.[12] Nevertheless, while breaking a potentially vicious cycle of uncontrolled elevated dietary intake is hypothesized to be beneficial for both BE symptoms and overweight,[12] BED and obesity seem to involve distinct neurobiological features.[21] Latest evidence shows that BED, but not obesity, is characterized by elevated sensitivity to food reward, coupled with increased impulsivity and compulsivity.[22] Likewise, emotional reactivity, featuring the intensity and duration of emotions in response to stimuli, is involved in eating-related psychopathology.[21,22] Furthermore, greater reported negative emotion is associated with subsequent BE in individuals with BED and not in overweight individuals without BED.[22] Hence, anti-obesity drugs might represent more of a symptomatic than a key treatment for BED, solely targeting weight management and not specific mechanisms underlying eating symptoms.[20] Furthermore, anti-obesity drugs seem to belong to the pharmacological group of image and performance-enhancing drugs, including a wide range of substances that are misused to enhance physical performance or appearance.[58] Among anti-obesity drugs, GLP-1 analogues, and notably semaglutide, can hold the potential to be misused by clinical and non-clinical populations to potentiate dietary restriction and pathological weight loss, which has led to an increased level of drug surveillance for monitoring abuse of this agent.[59-61] In addition, the illegal sale of these medications from unauthorized or rogue websites, along with their wide promotion through social media, might make this phenomenon difficult to curb.[59,62] Besides, highly prevalent comorbidity between SUDs and EDs, possibly attributable to shared psychopathological and neurophysiological pathways, could increase the risk of anti-obesity drugs misuse.[59,63] Finally, since evidence-based treatment for EDs requires the consumption of regular meals, anti-obesity drugs' effects on satiety/hunger could negatively impact ED treatment in susceptible subjects.[61] Overall, there is limited cross-referencing in most international treatment guidelines for EDs or obesity treatment, which curbs clinical guidance for BED patients with obesity.[8] In this context, it is thus crucial to raise awareness and provide resources to promote responsible prescribing practices, ultimately reducing the likelihood of misuse and abuse of these potentially valuable drugs.[60]

Conclusion

According to available evidence showing their impact on alleviating eating symptoms and decreasing body weight, most anti-obesity drugs might be considered a promising therapeutic option for people suffering from BED. Possibly, a better understanding of the specific mechanisms underlying BE psychopathology, also in terms of shared and distinct features characterizing BED and obesity respectively, will lead to a more focused use of anti-obesity drugs for BED. Although the utility of anti-obesity drugs seems grounded in a plausible biological rationale, additional evidence is needed, without underestimating the potential risks of their misuse in clinical as well as non-clinical populations.

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