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Review and Meta-analysis of Pharmacotherapy for Binge-eating Disorder

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This study evaluated available controlled treatment studies to determine utility of pharmacotherapy for binge-eating disorder (BED). The authors identified randomized placebo-controlled trials testing pharmacotherapy-only treatments and controlled trials testing pharmacotherapy with psychotherapy treatments. Meta-analysis was performed on placebo-controlled trials with data for attrition, remission, and weight loss. Qualitative review was performed on remaining controlled treatment literature. A total of 33 studies were considered of which 14 studies with a total of 1,279 patients were included in the meta-analysis of pharmacotherapy-only treatment and 8 studies with a total of 683 patients were included in the qualitative review of pharmacotherapy combined with psychotherapy interventions. No evidence suggested significant differences between medication and placebo for attrition. Evidence suggested that pharmacological treatments have a clinically significant advantage over placebo for achieving short-term remission from binge eating (48.7% vs. 28.5%) and for weight loss, although weight losses are not substantial. No data exist to allow evaluation of longer-term effects of pharmacotherapy-only treatment for BED. Combining medications with psychotherapy interventions failed to significantly enhance binge outcomes, although specific medications (orlistat, topiramate) enhanced weight losses achieved with cognitive behavioral therapy and behavioral weight loss. In summary, BED patients can be advised that certain pharmacotherapies may enhance likelihood of stopping binge eating short term, but that longer-term effects are unknown. Although some weight loss may occur, it is unlikely to be substantial with available medications. Combining medications with cognitive or behavioral treatments is unlikely to enhance binge outcomes, but specific medications (orlistat, topiramate) may enhance weight losses, albeit modestly.

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INTRODUCTION

Binge-eating disorder (BED), a research category in the *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV) (1), is characterized by recurrent binge eating without inappropriate weight-control behaviors. BED is a prevalent (2) and stable problem (3) associated with heightened psychological (4), psychosocial (2), psychiatric (5), and medical (6) impairment. BED is strongly associated with obesity (2), although obese persons with BED have significantly greater eating and psychological disturbances than obese persons without BED (7), and new evidence suggests that BED represents a distinct familial phenotype in obese individuals (8).

The first generation of treatment studies for BED identified some effective psychological treatments, as highlighted by critical qualitative reviews (9) and quantitative meta-analytic studies (10). In contrast, although a growing number of pharmacotherapy treatment studies have reported that certain medications have efficacy for BED, the clinical significance of this emerging literature is difficult to interpret due to mixed findings and methodological limitations. An early meta-analysis reported cautious support for selective serotonin reuptake inhibitor (SSRI) antidepressant medications (10), but the continued publication of randomized controlled trials (RCTs) testing various pharmacotherapies, including recent larger-scale studies, warrants a current critical review. The present study aimed to systematically evaluate the available controlled treatment research findings to determine the utility of pharmacotherapy-only treatments and pharmacotherapy combined with psychotherapy treatments for BED. This evaluation used a meta-analysis on placebo-controlled, pharmacotherapy-only trials that produced data for major outcomes (attrition, remission, and weight loss). Pharmacotherapy trials that included psychotherapy interventions were evaluated using a qualitative critical review.

METHODS AND PROCEDURES

Search strategy

We aimed to systematically identify and synthesize existing evidence for the use of pharmacological agents in the treatment of BED. Due to the relatively recent addition of BED as a research category to

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the DSM-IV (1), literature published prior to 1985 offered little to no clinical data specific to the current definition of BED. Accordingly, we attempted to locate all studies published between 1985 and 31 January 2008. To enhance the specificity of this review and to improve upon earlier shortcomings of qualitative reviews, we excluded literature pertaining to mixed eating disorder samples, nonpurging bulimia nervosa, atypical eating disorders, eating disorders not otherwise specified except for the specific example of BED, or the ICD-10 category, "overeating associated with other psychiatric condition" (11). Only randomized placebo-controlled trials evaluating the effects of a pharmacological agent as a primary treatment for BED (pharmacotherapy-only) or RCTs comparing pharmacotherapy vs. or combined with psychosocial treatments (additive or combined designs) were considered. Thus, all open-label trials and case series studies were excluded. A previously published RCT investigating d-fenfluramine (12) was also not considered in the meta-analysis because this medication was withdrawn from the market due to adverse events and safety concerns.

All eligible studies were examined for outcome data. As will be summarized below, data usable for meta-analysis for three major clinical outcomes (attrition, remission from binge eating, and weight loss) were reported by most pharmacotherapy-only studies. Due to the particularly wide scope of the additive or combined trials of pharmacotherapy and psychotherapy treatments, a critical qualitative review was performed in lieu of meta-analysis. Attrition was consistently defined as withdrawal or noncompletion for any reason, and remission was defined as 100% reduction in binge-eating episodes, although studies varied in the trial duration or required time frame. Attrition is a useful proxy for the general acceptability of a treatment. Remission from binge eating is a useful overall clinical outcome, although it does not necessarily capture other important aspects such as cognitive features of eating disorder psychopathology or associated psychological distress. Weight-change (continuous) data were reported by several studies and were included in the meta-analysis.

Relevant studies were identified with major computerized literature databases including: Medline, PubMed, PsychLit, Cochrane Library, and Science Direct. Relevant search terms included "binge", "binge eating", and "binge eating disorder." Studies were also identified by cross-referencing and hand-searching obesity, eating disorder, psychiatry, and pharmacology journals. A total of 33 studies were considered: 14 studies were included in the meta-analysis of pharmacotherapy-only studies and 19 were excluded for various methodological reasons (see **Table 1**). A summary of characteristics of pharmacotherapy-only studies used for the meta-analysis is provided (see **Table 2**). A total of eight controlled studies were qualitatively reviewed for outcomes to determine the utility of pharmacotherapy and psychotherapy interventions in additive/combined designs (see **Table 3**).

Data collection and analysis

Data were entered into RevMan 4.2.7, a statistical program developed by the Cochrane Collaboration (Review Manager, Version 4.2 for Windows; Cochrane Collaboration, Oxford, UK) for systematic reviews. Effect sizes for dichotomous data (remission, attrition) were evaluated by the relative risk, also referred to as risk ratio (RR), with 95% confidence intervals (CIs). Effect sizes for weight loss data were expressed as weighted mean differences (WMDs) using Hedges g ($ES = X_1 - X_2/S_{pooled}$) with a 95% CI. To increase power and precision, a summary variance-weighted effect size was calculated to lend more weight to larger studies. Whenever possible, intention-to-treat analyses were performed. For dichotomous remission data, missing data were treated based on the assumption of a negative outcome ("no remission achieved") and baseline values were carried forward. For continuous data, intention-to-treat data were used whenever possible; any completed-only data was clearly labeled to draw a distinction.

Heterogeneity was examined using a standardized χ^2 test and an I^2 test of heterogeneity, such that $I^2 < 30\%$ indicated mild heterogeneity, $I^2 =$ 30–50% indicated some heterogeneity, and $I^2 > 50\%$ indicated considerable heterogeneity. Results were synthesized using a fixed effects model for homogenous data or a random-effects model for heterogeneous data. If significant heterogeneity was found via graphical inspection or by I^2 tests, trials contributing to considerable heterogeneity were removed in sensitivity analyses and potential reasons accounting for such heterogeneity were discussed. Subgroup analyses were performed to compare efficacy across different medication classes. Forest plots are used to display the effect estimates and CIs for individual studies and meta-analyses; a statistically significant summary statistic (treatment effect size) is visually displayed by a CI falling entirely within the clinically relevant range and does not cross the line of no effect.

RESULTS

Pharmacotherapy-only studies: overview

Fourteen studies met the inclusion criteria and provided data eligible for at least one outcome measure of interest. **Table 2** provides a summary of each of the study's details including the nature of the sample, the design including dosing information and duration of the trial, and major outcomes such as attrition and clinical effects. A total of 1,279 participants (mostly women) were included across the 14 trials. Twelve of the studies were conducted in the United States, and one each in Brazil and Italy. Recruitment of participants was almost exclusively through media advertisement. Twelve of the fourteen RCTs were funded by the pharmaceutical industry (i.e., supported by the drug manufacturer), one (13) RCT did not disclose or acknowledge any funding source, and one (14) was funded by the National Institutes of Health, although medication and placebo pills were provided by the drug manufacturer.

Types of interventions included three main classes of drugs, including antidepressant SSRI/ serotonin–norepinephrine reuptake inhibitor medication, antiepileptic medication, and obesity medication. Seven trials were identified, which compared an SSRI antidepressant with placebo, including two studies of fluoxetine, two studies of fluvoxamine, one study of sertraline, one study of citalopram, and one study of escitalopram (14–19), and one trial compared a serotonin–norepinephrine reuptake inhibitor antidepressant with placebo (20). Three trials compared antiepileptic medications (topiramate and zonisamide) with placebo (21–23). Three trials compared obesity medication (sibutramine) vs. placebo (13,24,25). Some trials used flexible dosing of medication whereas others used fixed dosing throughout the course of treatment (**Table 2** describes dosing for all medications). The trials were of short duration, averaging 12.2 weeks with a range from 6 (refs. 17,18,26) to 24 weeks (25). To date, none have reported follow-up data after medication discontinuation.

Attrition: meta-analysis findings

Figure 1 summarizes attrition data which were provided by 13 of the 14 RCTs. In the placebo-treated condition, the overall attrition rate was 31.5%, compared with an overall attrition rate of 30.4% in the medication-treated condition. There was no evidence to suggest a clinically significant difference exists between medication and placebo for attrition ($N = 13$; $n = 1{,}254$; RR = 1.02: 95% CI: 0.79–1.32). For the SSRI subgroup, substantial heterogeneity was noted ($I^2 = 57.7\%$) and several sensitivity analyses were performed. The heterogeneity appeared due to the trial by Arnold *et al.* (26), which reported 57% attrition for the placebo group. Excluding this trial from

Table 1 Characteristics of clinical trials excluded from the meta-analysis of controlled pharmacotherapy-only trials

Study	Description	Reason for exclusion
Agras *et al.* (32)	Effect of desipramine vs. weight loss therapy and cognitive behavioral therapy (CBT) for overweight patients with binge-eating disorder (BED)	Additive design[b]
Appolinario *et al.* (47)	Open-label trial of topiramate for BED	No control group
Appolinario *et al.* (48)	Open-label trial of sibutramine in obese patients with BED	No control group
Bauer *et al.* (49)	Effect of sibutramine vs. placebo administered concurrently with CBT weight loss therapy for obese patients with and without subclinical binge eating	Subclinical disorder Additive design
Claudino *et al.* (27)	Double-blind randomized controlled trial (RCT) of topiramate vs. placebo administered concurrently with CBT for the treatment of BED	Additive design[b]
Devlin *et al.* (50)	Open-label trial of phentermine and fluoxetine as an adjunct to CBT for overweight patients with BED	No control group Additive design
Devlin *et al.* (29,51)	CBT and fluoxetine as adjuncts to behavioral weight loss therapy for BED	Additive design[b]
Golay *et al.* (30)	Double-blind RCT of orlistat vs. placebo in combination with a hypocaloric diet (600 kcal/day reduction to produce 0.25–0.5 kg loss per week) for BED and obesity	Additive design[b]
Grilo *et al*. (28)	Double-blind RCT of orlistat vs. placebo administered concurrently with CBT guided self-help for the treatment of BED	Additive design[b]
Guerdjikova *et al.* (19)	Case series of topiramate use with patients with BED and obesity following bariatric surgery	No control group
Kotwal *et al.* (52)	Lithium augmentation of topiramate for bipolar disorder with comorbid BED and obesity	No control group Bipolar disorder primary
Laederach-Hofmann *et al.* [a] (31)	Double-blind RCT of imipramine vs. placebo administered concurrently with diet counseling, behavioral therapy, and psychological supportive therapy	Additive design[b]
Malhotra *et al.* (53)	Open-label trial of venlafaxine for a series of overweight patients with BED	No control group
Marcus *et al.* (54)	RCT comparing fluoxetine vs. placebo plus behavior modification for obese binge eaters and nonbinge eaters. Patients classified as "binge eaters" using a self-report measure only	Uncertain diagnostic status Findings not provided separately for "binge eaters"
McCann and Agras (55)	RCT comparing desipramine with placebo for nonpurging bulimia nervosa (BN)	Diagnosis of BN, not BED
McElroy *et al.* (56)	Open-label trial of zonisamide for BED	No control group
Milano *et al.* (57)	RCT comparing sertraline with placebo for "binge eating disorder" (title) but report is clear that the subjects had BN and that the target symptoms were both binge eating and purging	Diagnosis of BN, not BED
Ricca *et al.* (33)	Comparison of fluoxetine or fluvoxamine combined with individual CBT for BED	No placebo control group Additive design[b]
Silveira *et al.* (58)	Open-label trial of reboxetine for obese patients with BED	No control group

[a]This study was included in the National Institutes of Clinical Excellence (2004) meta-analysis of pharmacotherapy only for BED. Review of the methodology in this study indicates that the double-blind placebo-controlled comparison of imipramine was performed with patients concurrently receiving biweekly diet counseling (30 min with a dietitian), biweekly psychological supportive therapy (15–25 min), plus three (1–1.5 h) behavioral group therapy sessions. [b]Study included in qualitative review of controlled trials with additive/combined designs (see Table 3).

the analysis resulted in a slight advantage to placebo for this subgroup analysis (RR = 1.66; 95% CI: 1.01–2.74; Z = 1.99; P =.05), but did not affect the pooled meta-analysis.

Effect of treatment on binge-eating remission: meta-analysis findings

Figure 2 summarizes remission data which was reported in 13 of the 14 RCTs. Two studies (14,16) defined remission as zero binges for past 28 days, whereas remaining studies used a less conservative definition of zero binges at end of treatment. Pooling all studies together, 48.7% of patients receiving medication achieved 100% remission from binge eating by the end of treatment, compared to 28.5% of patients receiving placebo. Overall, there was evidence to suggest a clinically significant difference exists between medication and placebo for remission, with medication being superior (N = 13; n = 1,254; RR = 0.74; 95% CI: 0.66–0.84). A relative risk of 0.74 indicates that medication reduces nonremission rates by ~26%.

When effect sizes for specific classes of medication were considered separately, there was also evidence to suggest a significant treatment effect relative to placebo, although the level of efficacy varied across subgroups. For SSRI medication (N = 7; n = 335; RR = 0.81; 95% CI: 0.70–0.94), antiepileptic medication (N = 3; n = 515; RR = 0.63; 95% CI: 0.51–0.78), and obesity (sibutramine) medication (N = 2; n = 364; RR = 0.80; 95% CI: 0.69–0.94), statistically significant summary statistic (RR) values were found with CIs that did not cross the line of no effect. The overall effect observed for antiepileptic agents with an RR

Table 2 Randomized placebo-controlled trials of pharmacotherapy-only treatment for binge-eating disorder

Study	Sample	Intervention	Recruitment/funding	Findings
Appolinario *et al.* (24)	*N* = 60 88% women Mean age 35.2 years (drug) 36.6 years (placebo) Mean weight 102.8 kg (drug) 98.7 kg (placebo)	Placebo-controlled, double-blind RCT of sibutramine Fixed dose of 15 mg/day 12-week trial No FUP data provided	Brazil Multisite Recruitment via media Pharmaceutical industry (drug manufacturer)	Attrition Overall dropout rate: 20% (12/60) Sibutramine: 23% (7/30) Placebo: 16% (5/30) Binge-eating frequency Sibutramine: binge-eating days decreased from 4.1 (1.8) to 1.4 (2.0) Placebo: binge-eating days decreased from 3.9 (1.8) to 2.3 (2.2) ($P = 0.03$) Weight loss Sibutramine: 7.4 kg loss Placebo: 1.4 kg gain ($P < 0.001$) Abstinence rates (100% binge-free) Sibutramine: 52% Placebo: 32% ($P = 0.40$)
Arnold *et al*. (26)	*N* = 60 93% women Mean age 41.9 years (drug) 40.8 years (placebo) Mean weight 39.6 BMI (drug) 36.7 BMI (placebo)	Placebo-controlled, double-blind, forced titration, flexible-dose RCT of fluoxetine Start dosage = 20 mg/day Increased to 80 mg/day, as tolerated End dosage mean = 71.3 mg/day 6-week trial No FUP data provided	United States Singlesite Recruitment via media Pharmaceutical industry (drug manufacturer)	Attrition Overall dropout rate: 40% (24/60) Fluoxetine: 23% (7/30) Placebo: 57% (17/30) Binge-eating frequency Fluoxetine: OBEs per week decreased from 6.0 to 1.8 Placebo: OBEs per week decreased from 6.1 to 2.7 ($P = 0.033$) Weight loss Fluoxetine: 3.9 kg loss (completer data) Placebo: 0.7 kg gain Abstinence rates (100% binge-free) Fluoxetine: 45% Placebo: 23.8% (n.s.)
Grilo *et al*. (14)	*N* = 54 (of a total *N* = 108) in only drug or placebo condition 78% women Mean age 44.3 years (drug) 43.6 years (placebo) Mean weight 38.9 BMI (drug) 35.7 BMI (placebo)	Placebo-controlled, double-blind RCT (2×2 balanced factorial design) comparing fluoxetine vs. placebo vs. cognitive behavioral therapy (CBT) plus fluoxetine vs. CBT plus placebo Fixed dosage of 60 mg/day 16-week trial No FUP data provided	United States Singlesite Recruitment via media National Institutes of Health Drug manufacturer provided medication and placebo pills but no support	Attrition Overall dropout rate: 18% (10/54) Fluoxetine: 22% (6/27) Placebo: 18% (4/27) Binge-eating frequency Fluoxetine: OBEs per month decreased from 20.0 to 11.0 Placebo: OBEs per month decreased from 16.3 to 7.4 (n.s.) Weight loss Fluoxetine: mean BMI decreased from 38.9 to 38.1 Placebo: no BMI change for placebo (n.s.) Abstinence rates (100% binge-free) Fluoxetine: 22% Placebo: 26% (ITT analyses; n.s.)
Guerdjikova *et al.* (19)	*N* = 44 97.7% women Mean age 36.9 years (drug) 41.0 years (placebo) Mean weight 40.1 (drug) 40.3 (placebo)	Placebo-controlled, double-blind, flexible-dose RCT of escitalopram Start dosage = 10 mg/day Increased to 30 mg/day, as tolerated End dosage mean = 26.5 mg/day 12-week trial No FUP data provided	United States Singlesite Recruitment via media Pharmaceutical industry (drug manufacturer)	Attrition Overall dropout rate: 23% (10/44) Escitalopram: 25% (5/20) Placebo: 17.3% (4/23) Binge-eating frequency Escitalopram: OBEs per week decreased from 4.9 to 0.9 Placebo: OBEs per week decreased from 5.1 to 1.7 (n.s.) Weight loss Escitalopram: 1.0 (2.6) kg Placebo: 0.6 (2.4) kg ($P < 0.001$) Abstinence rates (100% binge-free) Escitalopram: 50% Placebo: 26% (ITT analyses; n.s.)

Table 2 Continued on next page

Table 2 Randomized placebo-controlled trials of pharmacotherapy-only treatment for binge-eating disorder (Continued)

Study	Sample	Intervention	Recruitment/funding	Findings
Hudson *et al*. (16)	*N* = 85 90.5% women Mean age 41.2 years (drug) 43.0 years (placebo) Mean weight 34.2 BMI (drug) 36.8 BMI (placebo)	Placebo-controlled, double-blind, flexible-dose RCT of fluvoxamine Start dosage = 50 mg/day Increased to 300 mg/day as tolerated End dosage mean = 260 mg/day 9-week trial No FUP data provided	United States Multisite Recruitment via media Pharmaceutical industry (drug manufacturer)	Attrition Overall dropout rate: 21% (18/85) Fluvoxamine: 31% (13/42) Placebo: 12% (5/43) Binge-eating frequency Fluvoxamine: OBEs per week at baseline was 5.4 (2.9) Placebo: OBEs per week at baseline was 5.3 (2.5) Rate of reduction in OBE frequency was reported significant ($P < 0.001$) Weight loss Fluvoxamine: estimated mean loss was 2.7 lb (65-inch tall subject) Placebo: estimated mean loss was 0.3 lb ($P = 0.04$) Abstinence rates (100% binge-free) Fluvoxamine: 38% Placebo: 26% (ITT analyses; n.s.)
McElroy *et al*. (*17*)	*N* = 34 94% women Mean age 43.1 years (drug) 41.0 years (placebo) Mean weight 36.4 BMI (drug) 35.8 BMI (placebo)	Placebo-controlled, double-blind, flexible-dose RCT of sertraline Start dosage = 50 mg/day Increased to 200 mg/day as tolerated End dosage mean = 187 mg/day 6-week trial No FUP data provided	United States Singlesite Recruitment via media Pharmaceutical industry (drug manufacturer)	Attrition Overall dropout rate: 24% (8/34) Sertraline: 28% (5/18) Placebo: 19% (3/16) Binge-eating frequency Sertraline: OBEs per week decreased from 7.6 to 1.1 Placebo: OBEs per week decreased from 7.2 to 3.9 ($P < 0.01$) Weight loss Sertraline: estimated mean loss was 12.3 lb (65-inch tall subject) Placebo: estimated mean loss was 5.3 lb ($P < 0.01$) Abstinence rates (100% binge-free) Sertraline: 54% Placebo: 15% (completer data; n.s.)
McElroy *et al*. (18)	*N* = 38 95% women Mean age 42.0 years (drug) 39.2 years (placebo) Mean weight 41.4 BMI (drug) 34.2 BMI (placebo)	Placebo-controlled, double-blind, forced titration, flexible-dose RCT of citalopram Start dosage = 20 mg/day Increased to 60 mg/day, as tolerated End dosage mean = 57.9 mg/day 6-week trial No FUP data provided	United States Singlesite Recruitment via media Pharmaceutical industry (drug manufacturer)	Attrition Overall dropout rate: 18% (7/38) Citalopram: 16% (3/19) Placebo: 21% (4/19) Binge-eating frequency Citalopram: OBEs per week decreased from 5.2 to 1.7 Placebo: OBEs per week decreased from 5.7 to 3.4 ($P < 0.01$ for rate of reduction; endpoint analysis was nonsignificant) Weight loss Citalopram: mean BMI decreased from 41.1 to 40.9 Placebo: mean BMI increased from 34.2 to 35.7 ($P < 0.001$) Abstinence rates (100% binge-free) Citalopram: 47% Placebo: 21% (ITT analyses; n.s.)
McElroy *et al*. (21)	*N* = 61 87% women Mean age 40.9 years (drug) 40.7 years (placebo) Mean weight 44.2 BMI (drug) Unknown (placebo)	Placebo-controlled, double-blind, flexible-dose RCT of topiramate Start dosage = 25 mg/day Increased to 600 mg/day as tolerated End dosage median = 212 mg/day 14-week trial No FUP data provided	United States Singlesite Recruitment via media Pharmaceutical industry (drug manufacturer)	Attrition Overall dropout rate: 43% (16/61) Topiramate: 47% (14/30) Placebo: 39% (12/31) Binge-eating frequency Topiramate: OBEs decreased from 5.3 (2.8) at baseline to <1 OBE per week at 14 weeks Placebo: OBEs decreased from 6.3 (2.8) at baseline to <4 OBEs per week at 14 weeks Rate of reduction was reported significant ($P < 0.001$) Weight loss Topiramate: 5.9 kg Placebo: 1.2 kg ($P < 0.001$) Abstinence rates (100% binge-free) Topiramate: 64% Placebo: 30% ($P < 0.05$)

Table 2 Continued on next page

Table 2 Randomized placebo-controlled trials of pharmacotherapy-only treatment for binge-eating disorder (Continued)

Study	Sample	Intervention	Recruitment/funding	Findings
McElroy *et al*. (22)	*N*= 60 88% women Mean age 44.8 years (drug) 43.0 years (placebo) Mean weight 42.7 BMI (drug) 40.6 BMI (placebo)	Placebo-controlled, double-blind, flexible-dose RCT of zonisamide Start dosage = 100 mg/day Increased to 600 mg, as tolerated End dosage mean = 436 mg/day 16-week trial No FUP data provided	United States Singlesite Recruitment via media Pharmaceutical industry (drug manufacturer)	Attrition Overall dropout rate: 20% (12/60) Zonisamide: 27% (8/30) Placebo: 13% (4/30) Binge-eating frequency Zonisamide: OBEs decreased from 4.7 (1.4) to <2 OBEs per week at 16 weeks Placebo: OBEs per month decreased from 4.4 (2.0) to <2 OBEs per week at 16 weeks Rate of reduction was reported significant ($P = 0.02$) Weight loss Zonisamide: 4.8 kg lost Placebo: 1.0 kg lost ($P < 0.001$) Abstinence rates (100% binge-free) Zonisamide: 54% Placebo : 45% (ITT analyses; n.s.)
McElroy *et al*. (23)	*N* = 394 84% women Mean age 44.0 years (drug) 45.0 years (placebo) Mean weight 38.0 BMI (drug) 39.0 BMI (placebo)	Placebo-controlled, double-blind, flexible-dose RCT of topiramate Start dosage = 25 mg/day Increased to 400 mg over 8-week period, or as tolerated End dosage mean= 300 mg/day 16-week trial No FUP data provided	United States Multi-site study (19 centers) Recruitment via media and clinical referrals Pharmaceutical industry (drug manufacturer)	Attrition Overall dropout rate: 29% (114/394) Topiramate: 28% (55/195) Placebo: 30% (59/199) Binge-eating frequency Topiramate: OBEs per week decreased from 6.6 to 1.3 Placebo: OBEs per week decreased from 6.3 to 2.8 ($P < 0.001$) Weight loss Topiramate: 4.5 kg (5.1) loss Placebo: 0.2 kg (3.2) weight gain ($P < 0.001$) Abstinence rates (100% binge-free) Topiramate: 58% Placebo: 29% ($P < 0.001$)
McElroy *et al*. (20)	*N* = 40 83% women Mean age 43.1 years (drug) 39.2 years (placebo) Mean weight 37.3 BMI (drug) 41.4 BMI (placebo)	Placebo-controlled, double-blind, flexible-dose RCT of atomoxetine Start dosage = 40 mg/day Increased to 80 mg in second week Increased to 120 mg/day in third week, or as tolerated End dosage mean = 106 mg/day 10-week trial No FUP data provided	United States Singlesite Recruitment via media Pharmaceutical industry (funded in part by drug manufacturer)	Attrition Overall dropout rate: 38% (15/40) Atomoxetine: 30% (6/20) Placebo: 45% (9/20) Binge-eating frequency Atomoxetine: OBE frequency decreased from 4.2 (1.4) at baseline to <2 OBEs per week at 10 weeks Placebo: OBE frequency decreased from 4.9 (2.5) at baseline to <3 OBEs per week at 10 weeks Rate of reduction was reported significant ($P < 0.001$) Weight loss Atomoxetine: 2.7 (3.7) kg Placebo: 0.0 (3.2) kg ($P < 0.05$) Abstinence rates (100% binge-free) Atomoxetine: 70% Placebo: 32% ($P < 0.05$)
Milano *et al*. (13)	*N* =20 100% women Age range 24–36 years No baseline BMI data provided	Placebo-controlled, double-blind trial of sibutramine Fixed dose =10 mg/day 12-week trial No FUP data provided	Italy Singlesite Not reported Uncertain. No funding source was noted	Attrition 0% reported Binge-eating frequency Sibutramine: binge days per week decreased from 4.4 to 1.0 Placebo: binge days per week decreased from 4.7 to 4.4 ($P < 0.01$) Weight loss Sibutramine: 4.5 kg Placebo: 0.59 kg ($P < 0.01$) Abstinence rates (100% binge-free): n.r.

Table 2 Continued on next page

Table 2 Randomized placebo-controlled trials of pharmacotherapy-only treatment for binge-eating disorder (Continued)

Study	Sample	Intervention	Recruitment/funding	Findings
Pearlstein *et al*. (15)	*N* = 25 85% women Mean age = 41 years Mean BMI = 41.2	Placebo-controlled, double-blind, forced titration, flexible-dose RCT of fluvoxamine End dosage = 239 mg/day 12-week trial No FUP data provided	United States Singlesite Recruitment via media and referrals Pharmaceutical industry (drug manufacturer)	Attrition Overall dropout rate: 25% (5/20) Attrition was not reported separately for fluvoxamine and placebo Binge-eating frequency Fluvoxamine: binge days/28 days decreased from 14.7 to 3.1 Placebo: binge days/28 days decreased from 20.0 to 7.3 (n.s.) Weight loss Fluvoxamine: 1 lb loss Placebo: 4 lb gain (n.s.) Abstinence rates (100% binge-free) Fluvoxamine: >50% Placebo: >50% (n.s.)
Wilfley *et al*. (25)	*N* = 304 90% women Mean age 41.8 years (drug) 42.1 years (placebo) Mean weight 35.5 BMI (drug) 36.3 BMI (placebo)	Placebo-controlled, double-blind RCT of sibutramine Dosage = 15 mg/day 24-week trial No FUP data provided	United States Multisite (18 centers) Recruitment via media Pharmaceutical industry (drug manufacturer)	Attrition Overall dropout rate: 38% (115/304) Sibutramine: 32.9% (50/152) Placebo: 42.8% (65/152) Binge-eating frequency Sibutramine: OBEs per week decreased from 3.3 (1.5) to 0.6 (1.3) Placebo: OBEs per week decreased from 3.4 (2.0) to 1.2 (2.1) ($P < 0.001$) Weight loss Sibutramine: mean BMI decreased from 35.5 (5.8) to 33.9 (5.7) Placebo: mean BMI decreased from 36.3 (5.5) to 35.9 (5.7) ($P < 0.001$) Abstinence rates (100% binge-free) Sibutramine: 58.7% Placebo: 42.8% ($P < 0.001$)

FUP, follow-up period; ITT, intent-to-treat; OBEs, objective binge episodes; RCT, randomized controlled trial.

of 0.63 suggested that this broad class of medication reduces nonremission rates by 37%. Especially noteworthy in regard to antiepileptic agents given their different structures and mechanisms, are the RRs calculated for topiramate (0.56 and 0.59) in the two studies (21,23)—which suggest reduction of nonremission rates by 44–41%, respectively—being clearly stronger than the RR value (0.88) for zonisamide (e.g., 12%) (22). Findings for atomoxetine (serotonin–norepinephrine reuptake inhibitor) indicated a promising RR of 0.43, yet findings are limited to one trial ($n = 40$). A sensitivity analysis performed to exclude topiramate and atomoxetine yielded an overall RR of 0.81 (95% CI: 0.73–0.90; $I^2 = 0\%$], which suggests an average reduction of nonremission rates of 19% for 11 of the 14 pharmacotherapy-only RCTs.

Effect of treatment on BMI/weight: meta-analysis findings

Figure 3 summarizes data regarding effects on weight loss (kg) based on 8 of the 14 RCTs that provided usable data (i.e., weight-change data (m/s.d.) or actual pre- and post-treatment weight or BMI data (m/s.d.)). Overall, the pooled meta-analysis showed evidence of a significant additional weight reduction of 3.4 kg (7.5 lb) by medication compared to placebo ($N = 8$; $n = 1{,}236$; WMD = −3.42; 95% CI: −4.25 to −2.58). The effect sizes for the different medication classes varied considerably, from modest effects (WMD = −1.7) for SSRIs to larger effects for antiepileptic (WMD = −4.6) and antiobesity (WMD = −3.6) medications. Average mean weight loss for medication was 3.56 kg vs. 0.08 kg for placebo across the 14 trials. Overall, the average pretreatment weight (kg) for participants was 110 kg, or 240 lb, across studies; thus, observed percent weight loss achieved with medication equaled 3.2% (of original body weight).

Pharmacotherapy: combined or additive or relative effects

Eight RCTs that evaluated pharmacotherapy combined with psychotherapy interventions were identified. Table 3 provides a summary of each of the study's details. A total of 683 patients (~90% women) were included across the eight trials. Four of the studies were conducted in the United States, two in Switzerland, and one each in Brazil and Italy. Five studies were at single site, two had two sites, and one was multisite. Recruitment was through media advertisement in five studies and via clinic referral in three studies. Three of the eight trials were funded by the pharmaceutical industry (drug manufacturer), two did not disclose any funding, and three were funded by the National Institutes of Health or Medical Foundations.

The eight RCTs were diverse in their designs and treatment methods. Six studies provided double-blind data regarding medication vs. placebo delivered in addition to either cognitive behavioral therapy (CBT) (14,27,28), to diet (29,30),

Table 3 Summary of additive or combined trials of pharmacotherapy and psychotherapy treatment for BED

Study	Sample	Intervention	Recruitment/funding	Findings
Agras *et al*. (32)	*N* = 108 100% women Mean age: 45.0 years Mean BMI: 38.6	Randomized allocation to one of three treatments: behavioral weight loss (BWL) only for 9 months; cognitive behavioral therapy (CBT) for 3 months followed by BWL for 6 months; combination (CBT for 3 months followed by BWL for 6 months) plus desipramine added during last 6 months BWL delivered in 90-min group sessions following manualized protocol CBT delivered in 12 weekly group sessions following a manualized protocol Desipramine was given using flexible dosing as follows: 25 mg/day increased depending on side effects and therapeutic effects up to maximum of 300 mg/day. Mean dose of desipramine was 285 mg/day 9-month treatment 3-month FUP	United States Single-site study Recruitment via media National Institutes of Health	Attrition Overall dropout rate: 22% (24/108) BWL: 27% CBT-BWL: 17% CBT-BWL-desipramine: 23% Other findings Overall, the three treatment conditions did not differ on any measures either at the end of treatment or at follow-up At 3 months, CBT had significantly greater reduction in binge eating than the BWL while the BWL had significantly greater weight loss than CBT The addition of desipramine for the last 6 months did not lead to greater reduction in binge eating although statistically greater weight loss occurred compared to those without desipramine Thus, no evidence that either CBT or desipramine added to the effects of BWL
Claudino *et al*. (27)	*N* = 73 96% women Mean age 41.1 years (drug) 35.4 years (placebo) Mean weight 37.4 BMI (drug) 37.4 BMI (placebo)	Placebo-controlled, double-blind RCT comparing topiramate vs. placebo in combination with CBT After 2- to 5-week single-blind placebo run-in period, eligible patients received double-blind medication plus CBT delivered in 19 group sessions following manualized protocol Target dosing was 200 mg/day. Dosing scheduled as follows: 25 mg/day for 14 days, increased by 25 mg increments every 14 days up to 150 mg/day, increased weekly by 25 mg/day until target dose of 200 mg/day. Patients with limited clinical response in weight or binge eating were prescribed additional increments of 25 mg weekly until maximum dose of 300 mg/day was reached 21-week trial No FUP reported	Brazil Multi-site study Recruitment via media Pharmaceutical industry (drug manufacturer)	Attrition Overall dropout rate: 23% (17/73) Topiramate: 19% (7/37) Placebo: 28% (10/36) Binge-eating frequency CBT + topiramate and CBT + placebo did not differ significantly in rate of reduction for binge eating although 1-week (endpoint) remission rates were greater (84% vs. 61%; $P = 0.03$) Weight loss CBT + topiramate had significantly greater rate of weight loss than CBT + placebo (–6.8 kg vs. –0.9 kg; $P < 0.001$)
Devlin *et al*. (29)	*N* = 116 78% women Mean age: 43 years Mean weight: 115 kg	Placebo-controlled, double-blind RCT (2×2 balanced factorial design) comparing fluoxetine vs. placebo vs. CBT + fluoxetine vs. CBT + placebo all given in addition to BWL These four treatments were delivered in combination (in addition to) with group BWL treatment following manualized protocol CBT delivered in 16 individual sessions during the 20 weeks following manualized protocol Initial dosing of fluoxetine at 20 mg/day with increase to 60 mg/day after 4–5 weeks; flexible dosing <60 mg/day if needed to manage side effects 20-week acute treatment	United States Single-site study Recruitment via media National Institutes of Health (NIMH) Pharmaceutical industry (drug manufacturer provided medication and placebo and some research support)	Attrition Overall dropout rate: 36% CBT: 32% No CBT: 40% (n.s.) Fluoxetine: 28% Placebo: 45% ($P = 0.07$) Acute treatment Addition of CBT to BWL significantly enhanced reduction in binge-eating frequency ($P < 0.001$) and binge remission rates (62% vs. 33%; $P < 0.001$) relative to BWL without CBT The addition of fluoxetine to BWL did not result in significantly greater reduction in binge-eating frequency, binge remission (52% vs. 41%), or weight loss relative to BWL with placebo There were no significant main effects for either CBT assignment or medication assignment on weight loss at post-treatment There were no significant CBT by fluoxetine interactions

Table 3 Continued on next page

Table 3 Summary of additive or combined trials of pharmacotherapy and psychotherapy treatment for BED (Continued)

Study	Sample	Intervention	Recruitment/funding	Findings
Devlin *et al*. (52)	*N* = 114/116 patients from acute study were included in analyses of maintenance during 2-year FUP	Following initial 5-month acute treatment, a 2-year maintenance phase was offered. Maintenance treatment included double-blind medication for 18/24 months and monthly behavioral weight-control groups 24-month maintenance treatment	United States Single-site study Recruitment via media National Institutes of Health (NIMH) Pharmaceutical industry (drug manufacturer provided medication and placebo and some research support)	Attrition Overall dropout: 64% (74/116) attended at least one maintenance group; of these, the mean number of sessions attended was 11.3 Maintenance treatment Overall, the odds of binge remission 24-month post-treatment were ~1.4 the odds of remission post-treatment; there was no significant change in weight over the 24-month FUP Binge eating The addition of CBT, but not the addition of fluoxetine, to BWL resulted in significantly greater reductions in binge eating and binge remission rates at 24-month FUP Weight loss No significant main effects for either CBT or fluoxetine or significant CBT–fluoxetine interactions were observed for weight changes
Golay *et al*. (30)	*N* = 89 91% women Mean age 41.2 years (drug) 40.6 years (placebo) Mean weight 35.7 BMI (drug) 37.3 BMI (placebo)	Placebo-controlled, double-blind RCT comparing orlistat vs. placebo in combination with mildly hypocaloric diet Fixed dosage of 120 mg three times daily Hypocaloric diet prescribed individually. 600 kcal/day subtracted from estimated daily energy expenditure 24-week trial No FUP reported	Switzerland Two-site study Recruitment via clinics Pharmaceutical industry (drug manufacturer)	Attrition Overall dropout: 20% (18/89) Orlistat: 11% Placebo: 29% Binge eating Orlistat + diet and placebo + diet did not differ significantly in changes in binge frequency (5.4–1.0/week vs. 6.2–1.7/week) or proportion still meeting BED diagnosis Weight loss Orlistat + diet had significantly greater weight loss than placebo + diet (–7.4% vs. –2.3%; $P < 0.001$)
Grilo *et al*. (14) (see also Table 2 for summary of findings for *N* = 54 receiving pharma-cotherapy-only)	*N* = 54 (of a total *N* = 108) in combined CBT + fluoxetine (*n* = 26) or combined CBT + placebo (*n* = 28) 78% women Mean age 44.7 years (drug) 43.6 years (placebo) Mean weight 35.7 BMI (drug) 35.0 BMI (placebo)	Placebo-controlled, double-blind RCT (2×2 balanced factorial design) comparing fluoxetine vs. placebo vs. CBT + fluoxetine vs. CBT + placebo Fixed dosage of 60 mg/day CBT delivered in 16 individual weekly sessions following manualized protocol 16-week trial No FUP reported	United States Single-site study Recruitment via media National Institutes of Health (NIDDK) Drug manufacturer provided medication and placebo pills but no support	Attrition Overall dropout: 22% (12/54) CBT + fluoxetine: 23% CBT + placebo: 21% Binge eating In ITT analyses, 50% in CBT + fluoxetine vs. 61% in CBT + placebo had remission (n.s.) CBT + placebo and CBT + fluoxetine were both significantly superior to placebo-only and fluoxetine-only (see Table 2) OBE per month decreased from 22.7 to 4.2 in CBT + fluoxetine vs. 22.8 to 2.6 in CBT + placebo (n.s.) Reductions in OBE frequency in CBT + placebo and CBT + fluoxetine were both significantly superior to placebo-only and fluoxetine-only (see Table 2) Weight loss Mean BMI decreased from 35.7 to 34.9 in CBT + fluoxetine and from 35.0 to 34.2 in CBT + placebo (n.s.)
Grilo *et al.* (28)	*N* = 50 88% women Mean age 45.2 years (drug) 47.0 years (placebo)	Placebo-controlled, double-blind RCT comparing orlistat vs. placebo in combination with CBT delivered using guided self-help (CBTgsh) Fixed dosage of 120 mg three times daily	United States Single-site study Recruitment via media American Heart Association	Attrition Overall dropout: 22% (11/50) Orlistat: 24% Placebo: 20% (n.s.) Binge eating In ITT analyses, 64% in orlistat + CBTgsh vs. 36% in placebo + CBTgsh

Table 3 Continued on next page

Table 3 Summary of additive or combined trials of pharmacotherapy and psychotherapy treatment for BED (Continued)

Study	Sample	Intervention	Recruitment/funding	Findings
	Mean weight 36.2 BMI (drug) 36.8 BMI (placebo)	CBTgsh delivered using patient self-care CBT book plus six (15-min) individual sessions 12-week trial 12-week FUP		had remission ($P < 0.05$) at post-treatment and, at 3-month FUP, both had 52% (n.s.) Weight loss ITT rates for 5% weight loss were for orlistat + significantly higher CBTgsh than placebo + CBTgsh at post-treatment (36% vs. 8%) and 3-month FUP (32% vs. 8%)
Laederach-Hofmann *et al*. (31)	$N = 31$ 87% women Mean age 40.7 years (drug) 35.7 years (placebo) Mean weight 96.0 kg (drug) 114.8 kg (placebo)	Placebo-controlled double-blind RCT comparing imipramine vs. placebo in combination with diet counseling with psychological support Fixed dosage of 25 mg three times daily Biweekly (30 min) diet counseling plus biweekly (15–25 min) psychological supportive therapy plus three 1–1.5 h behavioral group therapy sessions 8-week trial 6-month open-phase FUP (medication blind broken, drug discontinued; dieting and psychological counseling continued)	Switzerland Single-site study Recruitment at a medical outpatient clinic. Existing medical charts reviewed and suitable patients invited to participate No funding source reported	Attrition Overall dropout: 6% (2/31) (1 from placebo and 1 from imipramine) Binge eating Imipramine + diet counseling and placebo + diet counseling resulted in statistically significant reductions in binge eating (7.1–2.8 binges per week vs. 7.1–5.4 binges per week) Weight loss The addition of imipramine resulted in significantly more weight loss (–2.2 kg vs. +0.2 kg; $P < 0.01$) at post-treatment and at FUP (–5.1 kg vs. +2.2 kg; $P < 0.001$)
Ricca *et al*. (33)	$N = 108$ 59% women Mean age: 25.9 years Mean BMI: 32.3	Controlled parallel-series open-label study compared five treatment conditions: CBT; CBT + fluoxetine; CBT + fluvoxamine; fluoxetine; fluvoxamine CBT delivered via 22 individual 50-min sessions Fluoxetine dosing as follows: 20 mg/day first week, 40 mg/day second week, and 60 mg/day for following 20 weeks; monthly medication visits Fluvoxamine dosing as follows: 100 mg/day first week, 100 mg twice daily during second week, and 100 mg t.i.d. for following 20 weeks; monthly medication visits 24-week trial 12-month FUP	Italy Two-site study Recruitment via two outpatient clinics No funding source reported	Attrition CBT: 15% CBT + fluoxetine: 27% CBT + fluvoxamine: 22% Fluoxetine-only: 24% Fluvoxamine-only: 27% Binge eating Binge frequency was significantly reduced from baseline to post-treatment and 12-month follow-up for CBT, CBT + fluoxetine, and CBT – fluvoxamine treatments ($P < 0.001$) but not in either the fluoxetine-only or the fluvoxamine-only groups Mean binge frequencies at the three time points: CBT (18, 8, 8); CBT + fluoxetine (17, 6, 7); CBT + fluvoxamine (18, 8, 8); fluoxetine (20, 19, 21); and fluvoxamine (20, 18, 18) Weight loss BMI was significantly reduced at post-treatment and at 12-month FUP for the CBT, CBT + fluoxetine, and CBT + fluvoxamine, but not in the fluoxetine-only or fluvoxamine-only treatments. CBT, CBT + fluoxetine, and CBT – fluvoxamine did not differ significantly

BED, binge-eating disorder; FUP, follow-up period; ITT, intent-to-treat; OBEs, objective binge episodes; RCT, randomized controlled trial.

or to multimodal diet plus psychosocial treatment (31). Two studies provided data regarding medication vs. CBT, delivered in combination with behavioral weight loss (BWL) (29,32) and one study provided separate data regarding two different medications (fluoxetine and fluvoxamine) vs. CBT and the addition of those two medications to CBT vs. CBT without medication (33). The trials tested various antidepressants including desipramine (32), imipramine (31), fluoxetine (14,29,33), fluvoxamine (33), obesity medication (orlistat) (28,30), and antiepileptic medication (topiramate) (27). Some trials utilized flexible dosing of medication, whereas others used fixed dosing throughout the course of treatment. The trials were of moderate duration, averaging 20.1 weeks of active acute treatment, with a range of 8 (ref. 31) to 36 (ref. 32) weeks. Five of the eight trials reported follow-up data for periods ranging 3–24 months following completion of treatment.

The heterogeneity of the designs of these studies precluded meaningful meta-analysis, although a qualitative review and synthesis of the findings (detailed in **Table 3**) follows. Overall, the addition of pharmacotherapy to CBT did not enhance binge-eating outcomes but might have enhanced weight loss outcomes. Specifically, the medications added to CBT in double-blind fashion (topiramate (27),

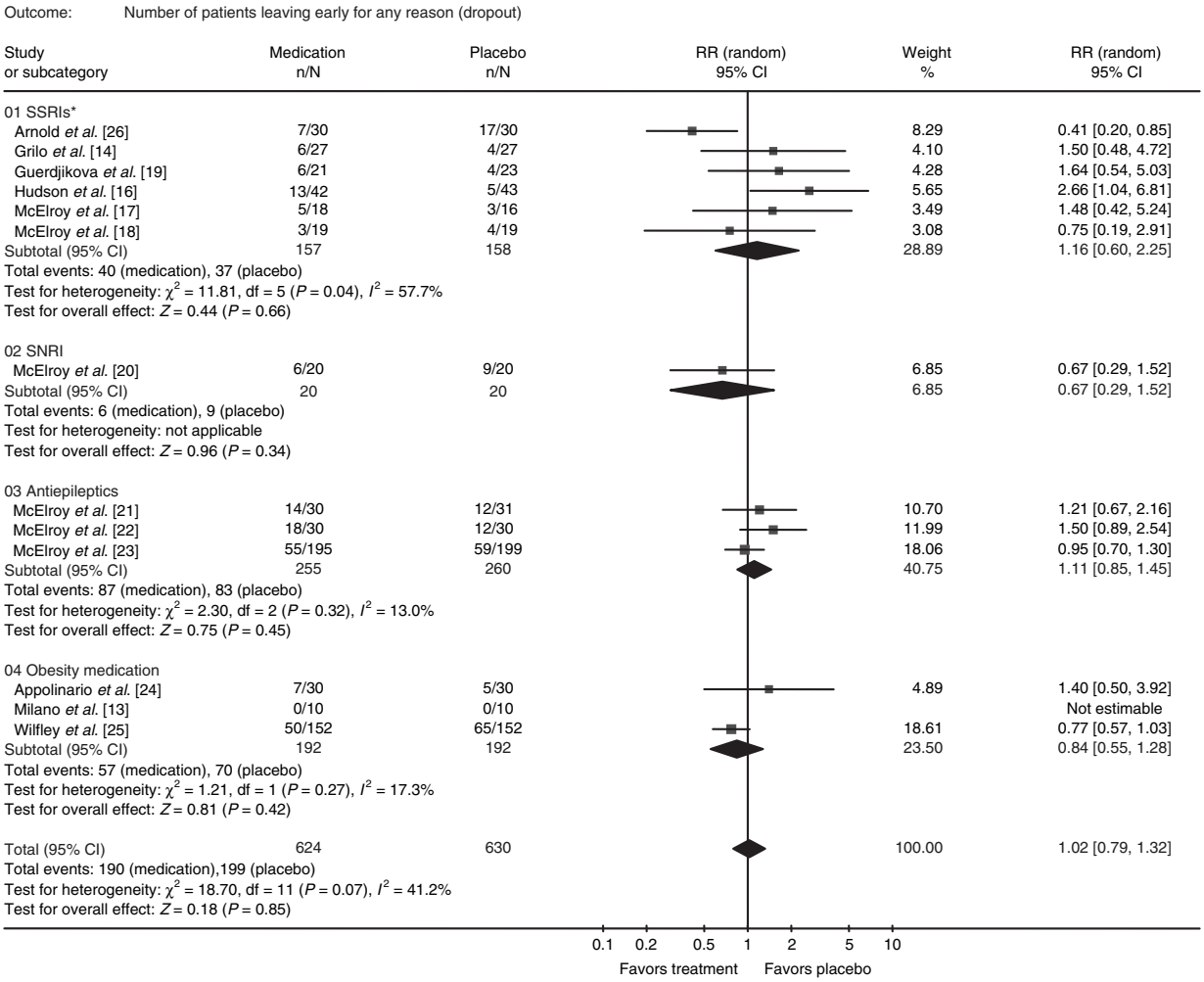

Figure 1 Attrition rate: medication vs. placebo. Pearlstein *et al.* (15) reported an overall (5/25) 20% dropout rate, but did not specify attrition by group (denoted by an asterisk).

fluoxetine (29), orlistat (28), imipramine (31)) did not significantly improve binge-eating outcomes, nor did the open-label addition of two SSRIs (fluoxetine and fluvoxamine) (33). In contrast, the addition of pharmacotherapy to CBT or to BWL resulted in mixed findings in terms of improving weight loss. Antidepressants including desipramine (32), fluoxetine (14,29,33), and fluvoxamine (33) did not significantly enhance weight losses in either CBT or BWL. In contrast, topiramate (27) and orlistat (28) enhanced weight losses in CBT, and imipramine (31) and orlistat (30) enhanced weight losses in diet and behavioral treatments. Noteworthy is that the addition of topiramate to CBT (27), and orlistat to diet (30), resulted in clinically significant (not just statistically) weight losses. Last, in terms of direct comparative data, two studies found that CBT (without medication) was superior to pharmacotherapy-only therapy with fluoxetine (14,33) or fluvoxamine (33).

DISCUSSION

The evidence base for pharmacotherapy for BED is growing, but remains limited both in terms of number of studies and particularly by the lack of follow-up findings regarding maintenance or durability of effects. Our tentative conclusions must be viewed cautiously in light of this relatively small literature and limited evidence base. Only 14 RCTs (placebo controlled) were identified that tested pharmacotherapy-only therapy as the primary intervention and only 8 RCTs were identified that tested pharmacotherapy relative to, or in combination with, psychotherapy interventions. There was no evidence to suggest a significant difference exists between medication and placebo for attrition, suggesting acceptability. Evidence exists to suggest that pharmacological treatments have a clinically significant advantage over placebo for achieving remission from binge eating and for producing weight loss, although the weight losses are not substantial (average percentage of weight loss was ~3% vs. 0%). There are no data to allow evaluation of longer-term effects or durability of pharmacotherapy-only therapy for BED. Combining medications with psychotherapy interventions failed to significantly enhance binge-eating outcomes, although promising findings have been reported for specific medications (orlistat and topiramate) to enhance weight losses, albeit modestly, achieved with CBT and BWL treatments.

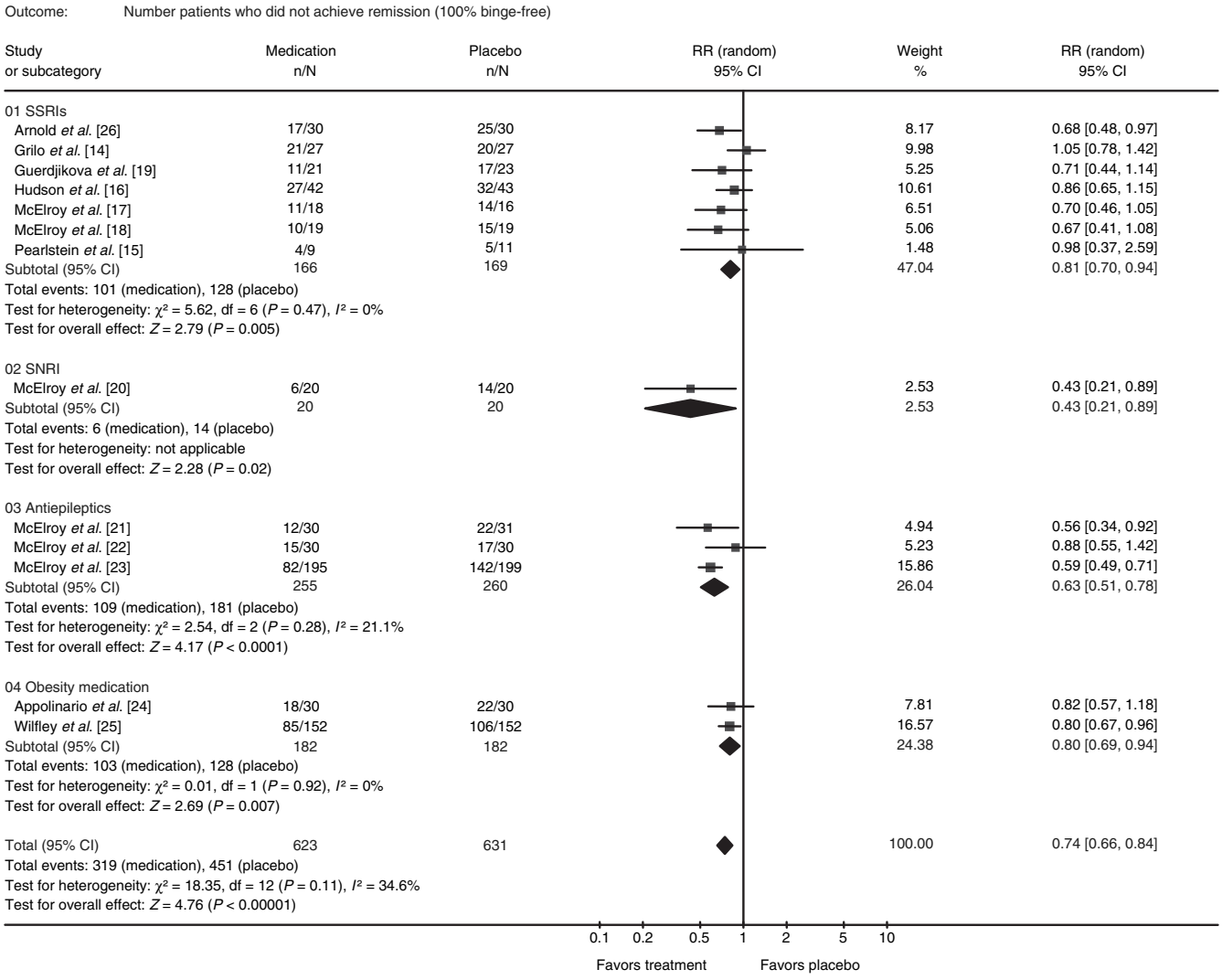

Figure 2 Remission rate: medication vs. placebo.

The literature on pharmacotherapy for BED is relatively small and should be cautiously interpreted within the context of potential methodological limitations. The RCTs for BED were of short duration (range 6–24 weeks) and none, to date, have reported follow-up data after medication discontinuation. This represents perhaps the major methodological limitation in the pharmacotherapy treatment literature for BED. The only study of pharmacotherapy-only therapy category with follow-up data (albeit for an obesity agent since withdrawn from the market due to adverse events) reported high relapse rates very soon after medication discontinuation (12). The literature varies in terms of following the reporting standards outlined by the CONSORT Group (34) for reporting RCT methodology (e.g., blinding methods) and detailing analyses although recent larger studies have generally improved in this regard. Pharmacotherapy RCTs, geared primarily toward addressing the important question, "Is there a drug effect?", tend to rely on statistical methods testing time to reduction or change in symptoms and sometimes do not report endpoint data. Most studies have not reported data regarding the effects of pharmacotherapy on eating disorder psychopathology (other than the behavioral feature of binge eating) characteristic of BED, such as unhealthy and chaotic eating patterns, body image dissatisfaction, and cognitive features such as the overvaluation of shape and weight (35).

The RCTs recruited almost exclusively from the community through media advertisements and enrolled primarily women (90% of participants were women), a departure from prevalence data suggesting a more even gender ratio (2). This raises the possibility of a clinic bias to the extent that media respondents to specialist research clinics might differ (in severity or complexity) from patients who present to traditional clinical services. Prevailing clinical lore is that recruited participants for such research studies are less severely disturbed and have fewer comorbidities than "real" clinic patients. Although surprisingly little evidence exists to address this potential criticism (36), inspection of exclusionary criteria in pharmacotherapy RCTs suggests that such concerns of a clinic bias may exist. Consider, for example, the two largest RCTs. McElroy and colleagues (23) excluded participants with current clinically

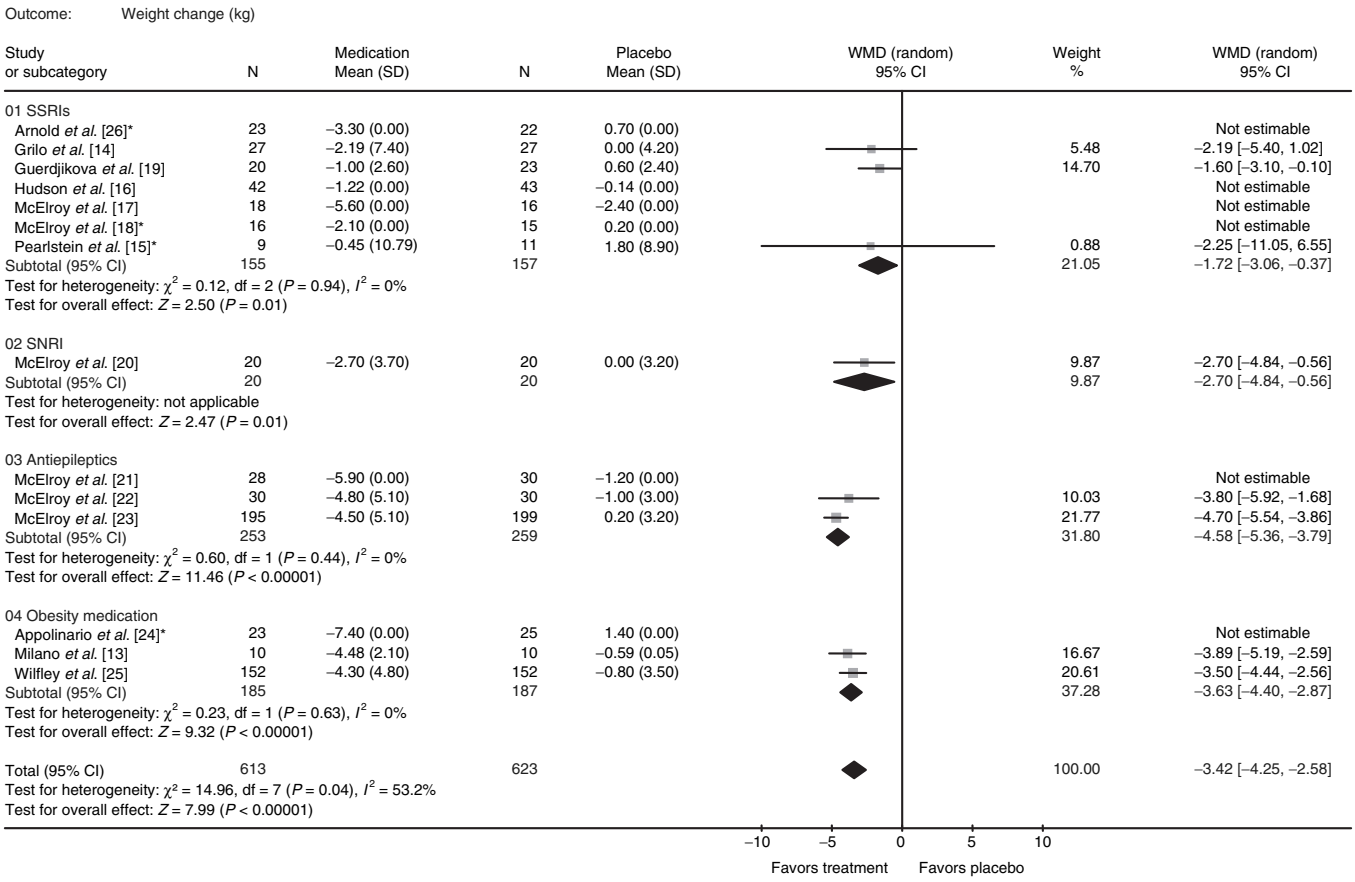

Figure 3 Weight loss (kg): medication vs. placebo. An asterisk (*) denotes completer data. When possible, missing or unavailable s.d. for change scores (*C*) were imputed using the general formulas: $\text{s.d.}(C) = \sqrt{(\text{s.d.}_{\text{pre}})^2 \times (\text{s.d.}_{\text{post}})^2 - (2 \times R_1 \times \text{s.d.}_{\text{pre}} \times \text{s.d.}_{\text{post}})}$. Pounds (lb) were converted to kilograms (kg) by multiplying values by 0.45.

significant depression, with current or recent substance abuse or dependence, and with personality disorders if there were concerns regarding assessment or compliance, and did not report a descriptive summary of psychiatric comorbidity in their subject description. Similarly, Wilfley and colleagues (25) excluded patients with drug or alcohol abuse during the past year and current major depressive disorder and did not report a descriptive summary of psychiatric comorbidity in their subject description. These exclusionary practices potentially limit generalizability, particularly because both epidemiological (2) and clinical (37,38) studies of psychiatric comorbidity in BED have reported that those exclusions are frequently co-occurring problems. Lastly, 12 of the 14 studies of pharmacotherapy-only category reported they were funded by the drug manufacturer. This state of affairs perhaps reflects, in part, difficulties faced by researchers in obtaining funding to perform treatment studies from the National Institutes of Health given its current severe budgetary shortfalls. Industry sponsorship may be relevant for clinicians and consumers of the literature (39,40) in light of recent reviews concluding that RCTs with pharmaceutical industry sponsorship and conflicts of interest were substantially more likely to report positive results in psychiatric (41) and biomedical (42,43) studies. Chan and colleagues (40) previously suggested that readers of original reports of RCTs funded by industry, as well as of reviews such as ours, should be cautious in interpreting conclusions given the potential for overestimation of efficacy.

With these potential methodological issues in mind, we cautiously offer implications for clinical practice and research. Clinically, our meta-analytic findings indicate patients with BED can be conservatively advised that certain pharmacotherapies may enhance the likelihood of remission from binge eating over the short term but that the longer-term effects of pharmacotherapy-only therapy are unknown. Patients should be advised that although some weight loss may occur, the amount is unlikely to be substantial with available pharmacological agents. Our meta-analytic findings generally echo the general conclusions regarding the potential utility of pharmacotherapy offered previously in the National Institutes of Clinical Excellence (NICE) guidelines (10), but suggest important changes in specific recommendations. That is, our findings highlight the potential utility of antiobesity (sibutramine) and antiepileptic (topiramate) medications, but suggest more limited utility of SSRIs, given their smaller effects on binge eating and absence of effect on weight. Alternative (nonpharmacological) treatments such as specific forms of psychotherapy (e.g., CBT and BWL) should be offered (9,10). Similarly, recent meta-analytic (44) and critical qualitative (45) reviews provided

cautious support for the use of certain self-help approaches. Self-help CBT provides an alternative first-step option to intensive psychosocial interventions that—like pharmacotherapy—is readily available. Our qualitative review highlighted that combining specific medications (orlistat and topiramate) with cognitive behavioral or BWL treatments, although unlikely to enhance binge-eating outcomes, may enhance weight losses, albeit modestly.

Implications for research include the need for additional large studies and longer studies with more comprehensive assessment protocols (46). In particular, there is a pressing need for RCTs of medications to include follow-up periods and to provide longer-term outcome data to address questions regarding the durability or maintenance of clinical effects. Such studies are needed to provide guidance regarding whether or when to discontinue pharmacotherapy. There is also a pressing need for secondary analyses of pharmacotherapy RCTs to explore for predictors, moderators, and mediators of outcome (9). Findings regarding predictors and moderators would have implications to guide rationale prescription of treatment, whereas findings regarding mediators would provide clues regarding mechanisms of action and the pathophysiological nature of BED.

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DISCLOSURE

The authors declared no conflict of interest.

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