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Binge-Eating Disorder in Adults:

A Systematic Review and Meta-analysis

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Abstract

Background—The best treatment options for binge-eating disorder are unclear.

Purpose—To summarize evidence about the benefits and harms of psychological and pharmacologic therapies for adults with binge-eating disorder.

Data Sources—English-language publications in EMBASE, the Cochrane Library, Academic OneFile, CINAHL, and ClinicalTrials.gov through 18 November 2015, and in MEDLINE through 12 May 2016.

Study Selection—9 waitlist-controlled psychological trials and 25 placebo-controlled trials that evaluated pharmacologic (n = 19) or combination (n = 6) treatment. All were randomized trials with low or medium risk of bias.

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Data Extraction—2 reviewers independently extracted trial data, assessed risk of bias, and graded strength of evidence.

Data Synthesis—Therapist-led cognitive behavioral therapy, lisdexamfetamine, and second-generation antidepressants (SGAs) decreased binge-eating frequency and increased binge-eating abstinence (relative risk, 4.95 [95% CI, 3.06 to 8.00], 2.61 [CI, 2.04 to 3.33], and 1.67 [CI, 1.24 to 2.26], respectively). Lisdexamfetamine (mean difference [MD], −6.50 [CI, −8.82 to −4.18]) and SGAs (MD, −3.84 [CI, −6.55 to −1.13]) reduced binge-eating–related obsessions and compulsions, and SGAs reduced symptoms of depression (MD, −1.97 [CI, −3.67 to −0.28]). Headache, gastrointestinal upset, sleep disturbance, and sympathetic nervous system arousal occurred more frequently with lisdexamfetamine than placebo (relative risk range, 1.63 to 4.28). Other forms of cognitive behavioral therapy and topiramate also increased abstinence and reduced binge-eating frequency and related psychopathology. Topiramate reduced weight and increased sympathetic nervous system arousal, and lisdexamfetamine reduced weight and appetite.

Limitations—Most study participants were overweight or obese white women aged 20 to 40 years. Many treatments were examined only in single studies. Outcomes were measured inconsistently across trials and rarely assessed beyond end of treatment.

Conclusion—Cognitive behavioral therapy, lisdexamfetamine, SGAs, and topiramate reduced binge eating and related psychopathology, and lisdexamfetamine and topiramate reduced weight in adults with binge-eating disorder.

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Binge-eating disorder (BED), the most common eating disorder, affects approximately 3% of U.S. adults in their lifetime (1–3). It is characterized by recurrent (≥1 per week for 3 months), brief (≤2 hours), psychologically distressing binge-eating episodes during which patients sense a lack of control and consume larger amounts of food than most people would under similar circumstances. Full diagnostic criteria are available in Appendix Table 1 (available at www.annals.org). Binge-eating disorder is more common in women (3.5%) than men (2.0%) and in obese individuals (5% to 30%) (4, 5), especially those who are severely obese and those seeking obesity treatment (3, 6). It typically emerges in early adulthood (1, 7) but may surface in adolescence (8) and persist well beyond midlife (9). In May 2013, the American Psychiatric Association (APA) officially recognized BED as a distinct eating disorder with a lower diagnostic threshold (in terms of frequency and duration of symptoms) than formerly accepted (10). The numbers of persons presenting for evaluation, receiving a BED diagnosis, and requiring treatment are expected to increase (11, 12).

BED is associated with poorer psychological and physical well-being, including major depressive and other psychiatric disorders (13, 14), relationship distress and impaired social role functioning (14–16), chronic pain (13, 14), obesity (13, 14, 17), and diabetes (18–21). Binge eating and BED predispose individuals to metabolic syndrome independent of weight gain (17), type 2 diabetes (22), earlier-onset diabetes (20), and worse diabetes-related complications and outcomes owing to nonadherence to recommended dietary modifications (23–25). Similarly, binge eating is implicated as a treatment-limiting factor in patients undergoing bariatric surgery, approximately 25% of whom experience “loss-of-control”

eating (26) that interferes with adherence to postsurgical nutritional recommendations and may impede weight loss and reduce quality of life (27, 28).

Treatment aims to reduce binge-eating frequency and disordered eating–related cognitions, improve metabolic health and weight (in patients who are obese, diabetic, or both), and regulate mood (in patients with coexisting depression or anxiety). Treatment approaches include psychological and behavioral treatments (hereafter "psychological"), pharmacologic treatments, and combinations of the 2 approaches. Table 1 describes common treatments for BED.

Current guidelines from the APA (29, 30) and the National Institute for Health and Care Excellence (NICE) (31) support the use of cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors, but they differ in content and timing. The APA recommends a team approach (including psychiatrists, psychologists, dietitians, and social workers) with CBT as the cornerstone and medication as adjunctive therapy. In contrast, NICE recommends a CBT-based self-help approach but also endorses medication monotherapy as sufficient treatment for some patients. Best practices for weight management are unclear, in part because of different perspectives on dieting-based approaches (32, 33) and bariatric surgery (34–37) in obese individuals with BED. Moreover, little is known about the effect of patient-, provider-, and setting-level factors on treatment outcomes.

Our group at the RTI International–University of North Carolina Evidence-Based Practice Center conducted a systematic review for the Agency for Health-care Research and Quality (AHRQ) (38) that updates and extends the scope of our 2006 AHRQ review on eating disorders (39, 40) by including studies of loss-of-control eating, examining nearly twice as many randomized, controlled trials (RCTs) of BED therapies, and applying meta-analytic techniques to measure BED treatment effectiveness.

Methods

Our methods, complete search strategies, and detailed evidence tables are available in the full systematic review (38). Our protocol (41) was guided by key questions reflecting previously identified evidence gaps, input from key informants and a technical expert panel, and analytic frameworks depicting treatment effectiveness and harms (Appendix Figure 1, available at www.annals.org). Key questions focused on the effectiveness of psychological treatments compared with waitlist, pharmacologic treatments compared with placebo, and combination treatments compared with placebo or waitlist. Primary outcomes were behavioral (reducing binge-eating frequency and increasing abstinence from binge eating), psychological (improving levels of eating-related and general psychological outcomes), and physical (reducing weight and improving other markers of health where relevant), and also included harms from treatment.

Data Sources and Searches

We searched EMBASE, the Cochrane Library, Academic OneFile, CINAHL, and ClinicalTrials.gov from inception to 18 November 2015, and MEDLINE from inception to

12 May 2016 (Supplement, available at www.annals.org). We hand-searched reference lists and relevant systematic reviews.

Study Selection

We used a PICOTS (populations, interventions, comparators, outcomes, timing, settings, and study designs) approach to identify studies that met our inclusion and exclusion criteria. The population of interest was adults with a diagnosis of BED based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth* or *Fifth Edition*. Interventions included pharmacologic, psychological, and behavioral treatments, as well as complementary and alternative medicine. We limited inclusion to RCTs that measured outcomes at the end of treatment or later in 10 or more randomly assigned patients; included active intervention, placebo, or waitlist control groups as comparators; were conducted in outpatient, inpatient, or home-based settings (such as self-help); and were published in English. We included trials conducted in any country. We selected abstracts for full-text review of articles if they met predefined inclusion and exclusion criteria (Appendix Table 2, available at www.annals.org). Two reviewers independently evaluated the full texts of selected articles to determine whether they should be included; disagreements were resolved by consensus discussion or with help from a third senior reviewer.

Data Abstraction and Risk-of-Bias Assessment

One reviewer abstracted details regarding study design, patient population, interventions and comparators, outcomes, duration of treatment and follow-up, settings, and results. A second reviewer checked the abstracted data for accuracy. For each study, 2 independent reviewers rated the risks of selection, performance, attrition, detection, and outcome reporting bias; they summarized their assessment overall as low, medium, or high risk of bias.

Statistical Analysis

For our investigation of treatments, we omitted studies with high risk of bias, except for harms and sensitivity analyses of meta-analyses. We graded the strength of evidence (SOE) for each major outcome with guidance from the Evidence-Based Practice Center regarding study limitations, consistency, precision, directness of the evidence, and risk of reporting bias (42, 43). The SOE grades are high, moderate, low, or insufficient, reflecting levels of confidence that the evidence represents the true effect. A grade of insufficient means that evidence either was unavailable or did not permit estimation of the effect. In this review, we report results with SOE grades of low, moderate, or high; see the technical report for more detailed results, including those with insufficient SOE (38).

For available trials using comparable treatment methods, durations, and outcomes, we performed an unadjusted random-effects meta-analysis using restricted maximum likelihood models (OpenMeta[Analyst] [Brown University Center for Evidence-Based Medicine]). Across studies, the percentage of patients achieving abstinence for each trial uses the number of all randomly assigned patients as the denominator to reflect a true intention-to-treat analysis (that is, to correct variations in results of modified intention-to-treat analyses from individual trials). We derived risk ratios (RRs) for abstinence (defined as 0 binge episodes recorded in the most recent assessment period, usually the past month) and mean

differences (MDs) for binge episodes per week, binge days per week, eating-related obsessions and compulsions, body mass index (BMI), weight, and depression scores. We assessed statistical heterogeneity using the I^2 statistic. In considering psychological studies for pooled analyses, we did not combine data from studies using different modes of delivery (for example, individual and group therapy) for the same treatment. If relevant, we conducted sensitivity analyses to measure the effect on pooled results of including studies rated high risk of bias. We also conducted qualitative syntheses of trials with interventions or outcomes that we judged insufficiently similar for meta-analysis.

Role of the Funding Source

This research was funded by AHRQ. Agency staff participated in developing the scope of the work, refining the analytic framework and key questions, resolving issues regarding the project scope, reviewing the draft report, and distributing it for peer review. AHRQ did not engage in selecting studies, assessing risk of bias, or synthesizing or interpreting data. The authors are solely responsible for the content and the decision to submit this manuscript for publication.

Results

Overview of Trials

We identified 34 trials with low or medium risk of bias (Appendix Figure 2 and Appendix Table 3, available at www.annals.org). Of these, 9 were waitlist-controlled psychological trials and 25 were placebo-controlled trials in which the active comparator was medication only ($n = 19$) or a combination treatment ($n = 6$). The psychological trials examined various forms of BED-focused CBT including self-help, psychodynamic interpersonal psychotherapy, dialectical behavior therapy, and behavioral weight loss treatment. The medication-only trials included anticonvulsants (topiramate and lamotrigine), antiobesity agents (orlistat), central nervous system stimulants (lisdexamfetamine), a dietary supplement (chromium picolinate), various second-generation antidepressants (SGAs; for example, citalopram, fluoxetine, and sertraline), and other medications (including acamprosate and armodafinil). Each of the 6 combination trials used a different behavioral plus medication approach.

Most trials (26 of 34) were conducted in the United States; the mean age ranged from 36 to 47 years, and most participants were female (≥77%), white, and overweight or obese (mean BMI, 28.8 to 41.1 kg/m^2). Trial sizes ranged from 24 to 394 randomly assigned participants, and treatment lasted 6 weeks to 6 months. Post-treatment follow-up assessments of the randomly assigned sample occurred in only 5 trials. Most studies excluded individuals receiving psychotropic medications; participants generally reported low to moderate levels of depression symptoms at baseline.

Sixteen trials contributed to the meta-analyses of key outcomes: 5 evaluated therapist-led CBT (44–48), 3 studied lisdexamfetamine (49–52), and 8 examined SGAs (fluoxetine, 60 mg/d [53] or 80 mg/d [54]; bupropion [55]; citalopram [56]; duloxetine [57]; escitalopram [58]; fluvoxamine [59]; and sertraline [60]). In these trials, 342 participants were randomly

assigned to therapistled CBT or a waitlist, 416 to an antidepressant or placebo, and 983 to lisdexamfetamine or placebo. Of 583 patients randomly assigned to the lisdexamfetamine groups, our analysis included 517 who received at least 50 mg/d, because this is the minimum dosage approved by the U.S. Food and Drug Administration for BED treatment. We qualitatively synthesized data for additional outcomes from these as well as the remaining 18 trials.

Outcomes

For each outcome, we first present the meta-analytic results in the text and supporting figures, then present the results of trials not included in the meta-analysis. Table 2 summarizes the qualitative findings for each trial, including the SOE grade for differences (or no differences) between interventions and comparators, which was low or moderate for all findings except one: weight reduction with lisdexamfetamine. Outcomes with insufficient SOE are not mentioned but may be found in the main report (38).

Binge-Eating Outcomes—More participants achieved abstinence from binge eating with therapist-led CBT versus waitlist (58.8% vs. 11.2%; RR, 4.95 [95% CI, 3.06 to 8.00]; I^2 = 0%; moderate SOE) (Figure 1), with lisdexamfetamine versus placebo (40.2% vs. 14.9%; RR, 2.61 [CI, 2.04 to 3.33]; I^2 = 0%; high SOE) (Figure 2, *top*), and with SGAs versus placebo (39.9% vs. 23.6%; RR, 1.67 [CI, 1.24 to 2.26]; I^2 = 0%; moderate SOE) (Figure 2, *bottom*). In addition, binge-eating frequency decreased with lisdexamfetamine (3 trials; MD in days/week −1.35 [CI, −1.77 to −0.93]; I^2 = 99.68; high SOE) and SGAs (7 trials; MD in episodes/week, −0.67 [CI, −1.26 to −0.09]; moderate SOE; I^2 = 0%; 3 trials; MD in days/week, −0.90 [CI, −1.48 to −0.32]; I^2 = 0%; low SOE). On the basis of qualitative syntheses, partially therapist-led CBT, guided self-help CBT, and topiramate increased binge-eating abstinence and reduced binge-eating frequency, and therapist-led CBT and structured self-help CBT reduced binge-eating frequency (Table 2).

Eating-Related Psychological Outcomes—Lisdexamfetamine (3 trials; MD, −6.50 [CI, −8.82 to −4.18]; I^2 = 99.86; moderate SOE) and SGAs (3 trials; MD, −3.84 [CI, −6.55 to −1.13]; I^2 = 44.11%; low SOE) reduced eating-related obsessions and compulsions. On the basis of qualitative analyses, topiramate decreased eating-related obsessions and compulsions and therapist-led CBT and guided self-help CBT consistently improved eating-related psychopathology, as reflected in participants' susceptibility to hunger; cognitive control over eating; and overall concerns about eating, shape, and weight (Table 2).

Symptoms of Depression and Other Psychological and Psychosocial Outcomes—SGAs significantly reduced scores on the Hamilton Rating Scale for Depression (HAM-D) (3 trials; MD, −1.97 [CI, −3.67 to −0.28]; I^2 = 48.62%; low SOE). Although individual pretreatment HAM-D scores ranged from 0 to 52, mean levels ranged from 2.6 to 5.7, leaving little room for clinically meaningful improvement. CBT (whether delivered in therapist-led, partially therapist-led, or structured self-help format) did not statistically significantly reduce depression symptoms (Table 2).

Weight-Related Outcomes—Trials varied in reporting weight and BMI as outcomes. SGAs did not significantly reduce either BMI (6 trials; MD, −1.02 [CI, −2.62 to 0.59]; I^2 = 0%) or weight (4 trials; MD in kilograms, −3.92 [CI, −10.16 to 2.33]; I^2 = 0%) (low SOE for no difference for both outcomes). On the basis of qualitative syntheses, reductions in BMI did not differ significantly between patients on waitlist and those receiving therapist-led, partially therapist-led, or structured self-help CBT (Table 2). In contrast, compared with placebo, lisdexamfetamine and topiramate resulted in greater weight reductions (Table 2). Several trials reported on weight-related metabolic variables; however, evidence was sufficient only for lisdexamfetamine reducing triglyceride levels compared with placebo (Table 2).

Harms Associated With Treatment

No psychological treatment studies reported harms. Of the 25 placebo-controlled medication-only or medication-plus-psychological intervention trials reviewed here, 20 reported on harms. Most involved medication side effects widely documented in non-BED populations. Four serious adverse events occurred in the 3 lisdexamfetamine trials.

In pooled analyses of 3 trials, lisdexamfetamine led to more insomnia (RR, 2.80 [CI, 1.74 to 4.51]; I^2 = 0%) and general sleep disturbances (RR, 2.19 [CI, 1.36 to 3.54]; I^2 = 31.65%) (both high SOE), as well as more headaches (RR, 1.63 [CI, 1.13 to 2.36]; I^2 = 0%), gastrointestinal upset (RR, 2.71 [CI, 1.14 to 6.44]; I^2 = 69.37%), and sympathetic nervous system (SNS) arousal (RR, 4.28 [CI, 2.67 to 6.87]; I^2 = 62.93%) (all moderate SOE). Qualitatively, the incidence of decreased appetite with lisdexamfetamine, SNS arousal with topiramate and flvoxamine, and gastrointestinal upset and sleep disturbance with fluvoxamine was greater than that observed with placebo (Appendix Table 4, available at www.annals.org).

Treatment was discontinued infrequently, but approximately twice as often among patients assigned to medication alone or to a combined intervention (n = 98; 13 of whom had a serious adverse event) than in the placebo group (n = 43; 7 of whom had a serious adverse event). Participants dropped out of psychological trials most often because of dissatisfaction.

Discussion

This review contributes new knowledge from an expanded treatment evidence base that permitted estimates of treatment effect sizes and harms from pooled analyses of therapist-led CBT, lisdexamfetamine, and SGAs not provided in our 2006 AHRQ report (39) or in other recent reviews published before May 2016 (74–82). Our review included 15 new RCTs (4 with CBT, 11 with medication) but excluded trials of sibutramine (which no longer is available in the United States), as well as studies of zonisamide, atomoxetine, and fluvoxamine that we rated as high risk of bias. Our findings provide strong support for therapist-led CBT, lisdexamfetamine, and SGAs (as a group) in helping patients with BED reduce binge-eating frequency and achieve abstinence; with less confidence, they suggest similar benefits from topiramate and other forms of CBT. Effect estimates varied in magnitude and cannot be compared easily across treatments because we could not do pooled

analyses on any single SGA and because the comparators for CBT and lisdexamfetamine differed (waitlist and placebo, respectively).

Patients seeking treatment for BED have various degrees of distress associated with binge eating–related obsessive thoughts and compulsions, worries about their shape and weight, and negative mood symptoms. With varying levels of certainty, our findings indicate that CBT in several formats, lisdexamfetamine, SGAs, and topiramate reduce these problems. The evidence from nearly 1000 patients was especially strong for lisdexamfetamine in reducing obsessions, compulsions, and weight. In overweight and obese individuals without BED, topiramate tends to induce weight loss (83), whereas SGAs tend to be weight-neutral (84), although individual responses to different SGAs may vary considerably. What remains unknown is whether reduced binge eating mediates weight loss in patients with BED treated with topiramate.

Despite the high levels of co-occurrence of BED with depression and other psychiatric conditions (85), we found no clear benefit of various forms of CBT in reducing symptoms of depression; limited evidence indicated a slight benefit with SGAs. This result may reflect 2 factors: Included trials generally comprised participants with low levels of negative mood symptoms at baseline (and not necessarily a clinical diagnosis of depression), and CBT was tailored to address problematic eating-related cognitions and behaviors unique to BED rather than global depressive cognitions and behaviors.

Although the number of serious treatment harms was extremely low, harms of any type, discontinuation of treatment attributed to harms, and the number of serious adverse events were approximately 2-fold greater among those receiving an active medication than among those receiving a placebo. Based on meta-analytic and qualitative results, harms occurred more frequently in patients treated with lisdexamfetamine, topiramate, or fluvoxamine than in those receiving a placebo. The most commonly reported harm in all trials, SNS arousal, occurred more than 4 times as frequently with lisdexamfetamine than placebo.

Clinicians should be aware of the potential for lisdexamfetamine to decrease appetite. Depending on a patient’s treatment goals and propensity toward food restriction, this side effect may be helpful or harmful and should be monitored closely. Cycling between dietary restraint and binge eating is common among individuals with BED (86–88); many restrict food intake during the day and binge eat in the evening. In addition, many individuals with BED experience deficits in appetite awareness (89, 90). Theoretically, the potential for harm may be greater among these groups.

In January 2015, lisdexamfetamine became the first (and only) drug approved by the U.S. Food and Drug Administration for treating patients with BED. A central nervous system stimulant and dextroamphetamine pro-drug, lisdexamfetamine is recognized widely as an effective treatment for reducing symptoms of impulsivity, inattention, and hyperactivity in children and adults with attention deficit–hyperactivity disorder, in whom it is well-tolerated with generally manageable side effects, such as dry mouth, restlessness, insomnia, and gastrointestinal upset (91). Our meta-analyses show tolerability and efficacy of lisdexamfetamine in BED, including clinically meaningful short-term reductions in binge-

eating frequency and in obsessive thoughts and compulsions regarding binge eating. Because the U.S. Drug Enforcement Administration classifies lisdexamfetamine as a Schedule II drug, individuals with a history of stimulant or other substance use disorder, suicide attempt, mania, or cardiac disease or abnormality were excluded from the trials; therefore, the results may not generalize to these BED populations.

In the United States, clinical practice guidelines tend to favor therapist-led CBT augmented with psychotropic medication (typically an antidepressant) as needed (29, 30). Many patients, however, have only limited access to BED-focused CBT with a BED-trained psychotherapist within a multidisciplinary team including a psychiatrist. The self-help approach recommended by NICE may be advantageous for overcoming this barrier to treatment access and increasing treatment dissemination. However, given the low SOE derived from our qualitative findings, recommending self-help CBT as first-line treatment would be premature. Our report cannot resolve the apparent discrepancy between the APA and NICE recommendations regarding when and how to integrate psychological, behavioral, and pharmacologic treatments for BED. Adequately powered head-to-head comparative effectiveness trials are needed to determine equivalence or noninferiority of self-help compared with therapist-led CBT.

Several limitations of the evidence base and review exist. The efficacy evidence base comprised only small samples or methodologically disparate single studies for nearly all medications, many psychological treatments, and all combination treatments. As a result, the evidence was insufficient to generate pooled estimates for self-help CBT or to evaluate the efficacy of specific antidepressants, promising interventions (such as interpersonal psychotherapy) (92, 93), complementary and alternative medicine or nutraceutical approaches, combination treatments (74, 82), or stepped-care strategies. Some trials had methodological limitations, including unclear randomization and allocation concealment, unmasked outcome assessors, and differential attrition between treatment groups. The instruments used to assess psychological outcomes, as well as how investigators reported outcomes, varied considerably. Moderate to high heterogeneity characterized the pooled estimates of some outcomes for some treatments, in several cases leading us to downgrade the SOE to moderate (for example, the effect of lisdexamfetamine on psychopathology and SNS arousal) or low (for example, the effect of SGAs on psychopathology). Studies did not report adverse events and discontinuations uniformly. Other limitations included trial setting (mainly supervised outpatient settings in U.S. academic research and medical centers) and population (mostly overweight or obese, 20- to 40-year-old white women with low levels of depression and anxiety), preventing us from assessing the effect of important patient characteristics, such as race, body weight, or presence of psychological or medical comorbidity, on treatment efficacy. Although publication bias and selective reporting were possible, many statistically nonsignificant results were reported in the trials, and a review of a sample of non-English abstracts ($n = 358$) and articles ($n = 9$) did not suggest a language bias or that any important psychological and medication trials were missing. Lastly, as no pharmacologic studies had long-term follow-up, persistence of efficacy benefits beyond active treatment could not be evaluated.

Among adults with BED, strong evidence indicates that therapist-led CBT, lisdexamfetamine, and SGAs as a general class (mainly selective serotonin reuptake inhibitors) reduce the frequency of binge eating, increase the likelihood of achieving abstinence from binge eating, and improve other eating-related psychological outcomes. Similar but less compelling evidence shows a benefit from other forms of CBT and topiramate. Harms associated with lisdexamfetamine, SGAs, and topiramate rarely limited treatment. It is unclear whether these findings generalize to patients with BED beyond those included in these trials (chiefly, overweight or obese 20- to 40-year-old white women without psychological or medical comorbidity). Adequately powered trials are needed to evaluate the *comparative* long-term benefits of psychological and pharmacologic treatments. Given the high levels of association among BED, obesity, and depression, future studies should determine whether certain treatments are better suited for particular subsets of patients.

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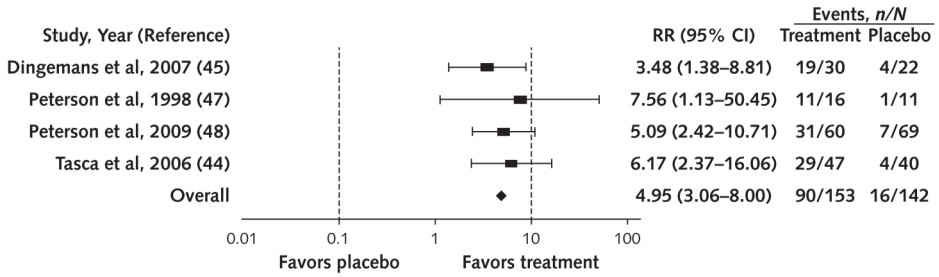


Figure 1.

Effect of therapist-led cognitive behavioral therapy on abstinence from binge eating.

RR = risk ratio.

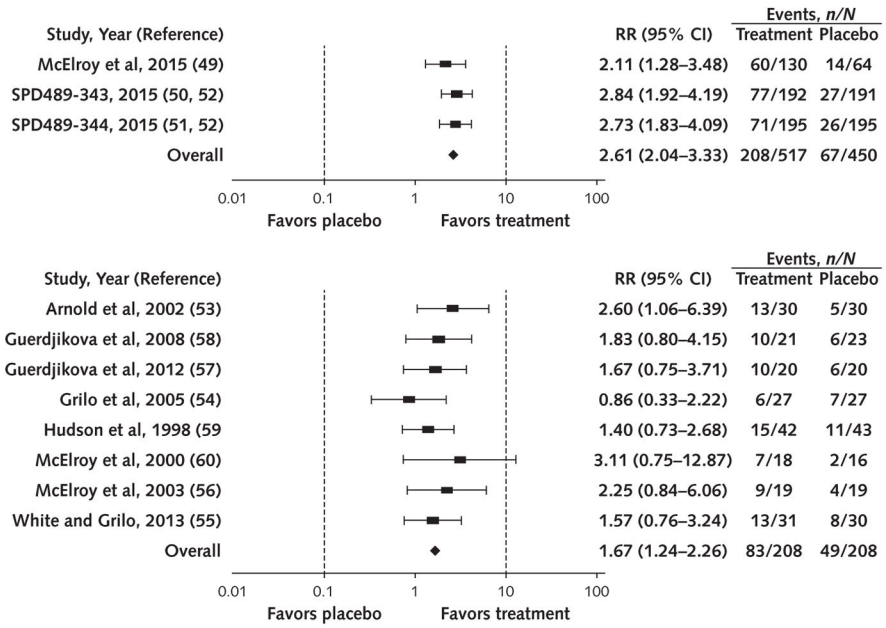
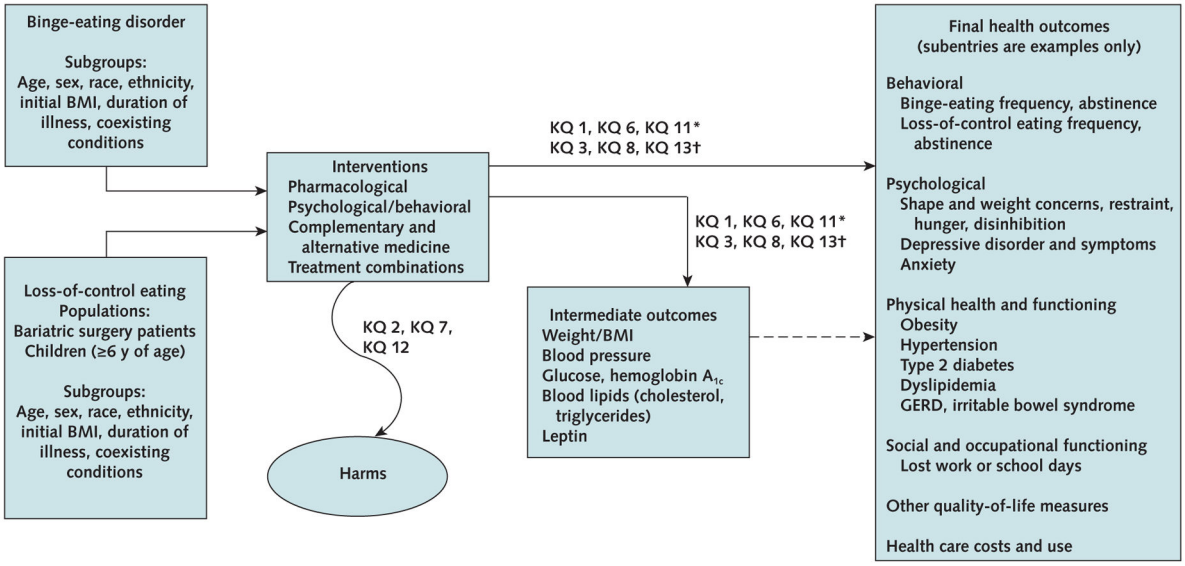


Figure 2.

Effect of lisdexamfetamine, 50 or 70 mg/d (*top*), and second-generation antidepressants (*bottom*) on abstinence from binge eating.

RR = risk ratio.



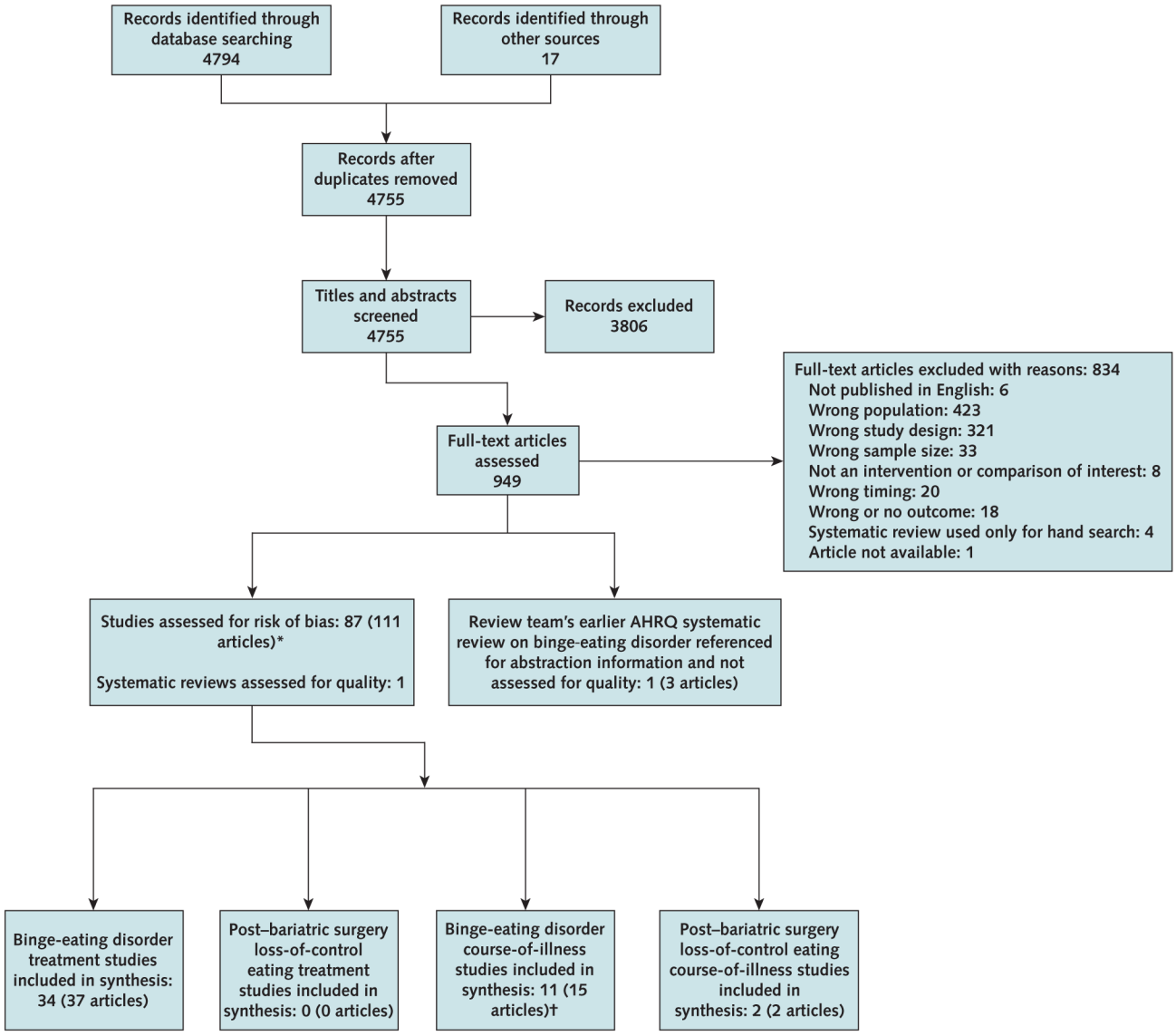
Appendix Figure 1.

Analytic framework for treatment effectiveness and harms.

BMI = body mass index; GERD = gastroesophageal reflux disease; KQ = key question.

* Effectiveness of treatment.

† Differences between subgroups.



Appendix Figure 2.

Flow diagram.

AHRQ = Agency for Healthcare Research and Quality.

* The figure was adapted from a larger report. Not all studies assessed for risk of bias are accounted for at the bottom of the figure because some populations are not included in the analysis in this article.

† Three studies (3 articles) also are included for binge-eating disorder treatment (key questions 1, 2, and 3) synthesis.

Table 1

Interventions Commonly Used in Treating Patients With Binge-Eating Disorder

Treatment	Description
Psychological, behavioral, or both	
CBT	Focuses on identifying relationships among thoughts, feelings, and behaviors; aims to reduce negative emotions and undesirable behavior patterns by changing negative thoughts about oneself and the world. CBT may be delivered in various forms according to the level of therapist involvement—e.g., from therapist engaged in all aspects of treatment (therapist-led CBT) to no therapist engagement (self-help CBT). In self-help CBT, the patient follows a treatment manual or book, either with the help of a facilitator (e.g., guided or structured self-help) or alone. CBT may be tailored to the patient by focusing on problematic eating-related cognitions and behaviors.
Dialectical behavior therapy	Focuses on increasing mindfulness and developing skills to improve emotion regulation, distress tolerance, and interpersonal relationships to help patients respond to stress and negative affect more effectively.
Interpersonal psychotherapy	Focuses on identifying and changing the role of interpersonal functioning in causing and maintaining negative mood, psychological distress, and unhealthy behaviors.
Behavioral weight loss	Incorporates various behavioral strategies to promote weight loss, such as restricting caloric intake and increasing physical activity.
Pharmacologic	
Antidepressants	Selectively inhibit reuptake of neurotransmitters involved in regulating mood and appetite (i.e., dopamine, norepinephrine, and serotonin). Common examples include bupropion, citalopram, desipramine, duloxetine, fluoxetine, fluvoxamine, and sertraline, which are indicated for treating patients with depression.
Anticonvulsants	Indicated for treating patients with epilepsy, bipolar disorder, major depression, and migraines. Topiramate, a carbonic anhydrase inhibitor, is the most commonly used.
Antiobesity agents	Used to treat obesity. For example, orlistat inhibits pancreatic lipase and thus decreases fat absorption in the gut.
Central nervous system stimulants	Generally used to enhance or accelerate mental and physical processes; specifically used to treat attention deficit–hyperactivity disorder and certain sleep problems. Lisdexamfetamine, the only U.S. Food and Drug Administration–approved medication for binge-eating disorder, belongs to this class.

CBT = cognitive behavioral therapy.

Table 2

Treatment Effectiveness for Binge-Eating Disorder: Qualitative Synthesis Results

Intervention and Outcome	Reference	Trials, *n*	Participants, *n*	Summary of Findings Measured at the End of Treatment	Strength of Evidence
Abstinence from binge eating					
CBT-PTL	47, 48	2	162	Greater percentage achieved abstinence with CBT-PTL vs. waitlist: 68.8% vs. 12.5% (47)†; 33% vs. 10% (48)†	Low for benefit
CBTgsh	61, 62	2	122	Greater percentage achieved abstinence with CBTgsh vs. waitlist: 35.1% vs. 8.1% (61)†; 50% vs. 8% (62)†	Low for benefit
Topiramate	63, 64	2	468	Greater percentage achieved abstinence with topiramate vs. placebo: 58% vs. 29% (63)†; 64% vs. 30% (64)†	Moderate for benefit
Binge-eating frequency					
CBT-TL	45, 47, 48	3	208	Greater change in episodes/wk with CBT-TL vs. waitlist: −9.3 vs. −1.6 (45); −2.7 vs. +1.2 (47)†; −18.3 vs. −5.5 (48)†	Moderate for benefit
CBT-PTL	47, 48	2	162	Greater reduction in episodes/wk with CBT-PTL vs. waitlist: −4.2 vs. +1.2 (47)†; −12.2 vs. −5.5 (48)†	Low for benefit
CBTssh	47, 48	2	162	Greater reduction in episodes/wk with CBTssh vs. waitlist: −2.7 vs. +1.2 (47)†; −10.5 vs. −5.5 (48)†	Low for benefit
CBTgsh	61, 62	2	122	Greater reduction in episodes/wk with CBTgsh vs. waitlist: −11.9 vs. −5.7 (61)†; −13.5 vs. −8.1 (62)†	Low for benefit
Topiramate	63, 64	2	468	Greater reduction in episodes/wk with topiramate vs. placebo: −5.0 vs. −3.4 (63); −5.0 vs. −2.9 (64)†	Moderate for benefit
Eating-related psychopathology					
CBT-TL	44–48			Greater improvement with CBT-TL vs. waitlist based on consistent changes across key measures of eating-related psychopathology	Moderate for benefit
		2	181	Decrease in EDE global score: −1.1 vs. 0 (45)†; −0.7 vs. −0.3 (48)	
		3	263	Decrease in TFEQ hunger: −1.50 vs. −0.30 (48); −2.29 vs. +0.13 (46); −2.59 vs. −0.41 (44).† A fourth study (47) reported a statistically significant difference but no data.	
		2	175	Decrease in TFEQ disinhibition: −2.40 vs. −0.20 (48)†; −2.96 vs. −1.00 (46).† A third study (47) reported a statistically significant difference but no data.	

Intervention and Outcome	Reference	Trials, *n*	Participants, *n*	Summary of Findings Measured at the End of Treatment	Strength of Evidence
		3	263	Increase in TFEQ cognitive restraint: 1.83 vs. −1.67 (44)†; 1.90 vs. 0.10 (48); 2.74 vs. 2.50 (46). A fourth study (47) reported a statistically nonsignificant difference but no data.	
CBTgsh	61, 62	2	122	Greater decrease in EDE-Q global score with CBTgsh vs. waitlist: −1.1 vs. −0.4 (61)†; −1.5 vs. −0.1 (62)†	Low for benefit
Topiramate	63, 64	2	468	Greater decrease in YBOCS-BE total score with topiramate vs. placebo: −14.3 vs. −7.9 (63)†; authors reported greater rate of reduction ($P < 0.001$) (64)	Moderate for benefit
Symptoms of depression and other psychological and psychosocial outcomes					
CBT-TL	44–48			CBT-TL not superior to waitlist for reducing depression symptoms based on the following differences (4 of 5 differences were statistically nonsignificant)	Low for no difference
		2	98	BDI: −4.5 vs. −6.5 (46); −7.8 vs. −0.3 (45)†	
		1	27	HDRS: −5.0 vs. NR (authors reported no difference; $P = 0.58$) (47)	
		1	129	IDS-SR: −4.4 vs. −3.1 (48)	
		1	88	CESD: −6.16 vs. −0.54 (44)	
CBT-PTL	47, 48			CBT-PTL not superior to waitlist for reducing depression symptoms based on the following statistically nonsignificant differences	Low for no difference
		1	30	HDRS: −5.5 vs. NR (authors reported no difference; $P = 0.58$) (47)	
		1	132	IDS-SR: −2.7 vs. −3.1 (48)	
CBTssh	47, 48			CBTssh not superior to waitlist for reducing depression symptoms based on the following statistically nonsignificant differences	Low for no difference
		1	26	HDRS: −4.5 vs. NR (authors reported no difference; $P = 0.58$) (47)	
		1	136	IDS-SR: −3.3 vs. −3.1 (48)	
Weight and weight-related outcomes					
CBT-TL	44–48	5	342	CBT-TL (range, −0.1 to +1.6) not statistically significantly different than waitlist (range, −0.95 to +0.20) for reducing BMI	Moderate for no difference
CBT-PTL	47, 48	2	162	CBT-PTL not statistically significantly different than waitlist for reducing BMI: +0.4 vs. NR (authors reported no difference; $P = 0.127$) (47); −0.1 vs. +0.2 (48)	Low for no difference
CBTssh	47, 48	2	162	CBTssh not statistically significantly different than waitlist for reducing BMI: −4.5 vs. NR (authors reported no difference; $P = 0.127$) (47); −3.3 vs. −3.1 (48)	Low for no difference

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Intervention and Outcome	Reference	Trials, *n*	Participants, *n*	Summary of Findings Measured at the End of Treatment	Strength of Evidence
Lisdexamfetamine *	49, 52	3	966	Greater percentage weight loss with 50 or 70 mg/d lisdexamfetamine than with placebo. Study 1 (49): −5.2% †; study 2 (52): −6.35% †; study 3 (52): −5.41% †	High for benefit
		2	724	Greater reduction in triglycerides with 50 or 70 mg/d lisdexamfetamine vs. placebo. Study 2 (52): −0.199 mmol/L (95% CI, −0.310 to −0.088 mmol/L) †; study 3 (52): −0.196 mmol/L (CI, −0.321 to −0.0070 mmol/L) †	Moderate for benefit
Topiramate *	63, 64	2	468	Greater weight loss with topiramate vs. placebo: −4.5 vs. +0.2 kg (63) †; −5.9 vs. −1.2 kg (64) †	Moderate for benefit

BDI = Beck Depression Inventory; BMI = body mass index; CBTgsh = cognitive behavioral therapy, guided self-help; CBT-PTL = cognitive behavioral therapy, partially therapist-led; CBTssh = cognitive behavioral therapy, structured self-help; CBT-TL = cognitive behavioral therapy, therapist-led; CESD = Center for Epidemiologic Studies Depression Scale (65); EDE = Eating Disorder Examination (66); EDE-Q = Eating Disorder Examination Questionnaire (67); HDRS = Hamilton Depression Rating Scale (68); IDS-SR = Inventory of Depressive Symptoms Self-Report (69, 70); NR = not reported; TFEQ = Three-Factor Eating Questionnaire (71); YBOCS-BE = Yale–Brown Obsessions and Compulsions Scale, adapted for binge eating (72, 73).

*To convert triglyceride levels to mg/dL, divide by 0.0113.

†Treatment difference was reported by the study authors to be statistically significant.

Appendix Table 1

DSM-5 Diagnostic Criteria for Binge-Eating Disorder

Definition, by Criteria Set
Criterion 1
Recurrent episodes of binge eating characterized by both of the following:
a. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period under similar circumstances
b. Sense of a lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)
Criterion 2
Binge-eating episodes are associated with 3 (or more) of the following:
a. Eating much more rapidly than normal
b. Eating until feeling uncomfortably full
c. Eating large amounts of food when not feeling physically hungry
d. Eating alone because of being embarrassed by how much one is eating
e. Feeling disgusted with oneself, depressed, or very guilty after overeating
Criterion 3
Marked distress regarding binge eating is present.
Criterion 4
Binge eating occurs, on average, at least 1 d/wk for 3 mo
Criterion 5
Binge eating is not associated with regular use of inappropriate compensatory behavior (e.g., purging, fasting, excessive exercise) and does not occur exclusively during the course of anorexia nervosa or bulimia nervosa.
Severity grading, *episodes/wk*
Mild: 1–3
Moderate: 4–7
Severe: 8–13
Extreme: ≥14

DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (10).

Appendix Table 2

Inclusion and Exclusion Criteria *

Category	Criteria	
	Inclusion	**Exclusion**
Population	Individuals of all races, ethnicities, and cultural groups who met DSM-IV or DSM-5 criteria for BED	Co-occurring anorexia nervosa or bulimia nervosa RCTs with fewer than 10 participants and nonrandomized studies with fewer than 50 participants
Interventions	Psychological, behavioral, pharmacological, or CAM treatments or combinations of treatments	Pharmacologic interventions not approved for marketing in the United States
Comparators	Any active intervention described in the PICOTS criteria, placebo, or usual care	Pharmacologic interventions not approved for marketing in the United States
Study duration	No limit	None
Settings	No limit; studies include inpatient, outpatient, or home-based settings for treatments such as self-help	None
Outcomes	Intermediate and final health outcomes, and treatment harms. Intermediate health outcomes including biomarkers that can be linked directly to final physical health outcomes, such that an accumulation or worsening over time in that biomarker would result in the final health outcome	Studies that did not include at least 1 of the outcomes
Timing of outcome measurement	End of treatment or later	Outcome measurement before study completion only

BED = binge-eating disorder; CAM = complementary and alternative medicine; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (10); DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition;* PICOTS = populations, interventions, comparators, outcomes, timing, and setting; RCT = randomized, controlled trial.

* These criteria are a subset of those used in the full report (38), which included populations of individuals with loss-of-control eating and outcomes reflecting the course of illness.

Appendix Table 3

Baseline Characteristics of the Included BED Treatment Effectiveness Trials ($n = 34$)

Study, Year (Reference); Country	Intervention and Comparators; Randomly Assigned Participants, n	Treatment Duration	Mean Age (SD), y	Mean BMI (SD), kg/m^2	Female, %	Nonwhite, %	Current Axis I Diagnosis, %	Risk of Bias
Trials contributing to the meta-analyses ($n = 16$)								
Psychological interventions ($n = 5$)								
Dingemans et al., 2007 (45); Netherlands	G1: CBT-TL *; 30 G2: Waitlist; 22	20 weeks	38.8 (10.4) 36.4 (11.3)	NR	94.23	NR	Mood disorder: 16 Anxiety: 17	Medium
Eldredge et al., 1997 (46); United States	G1: CBT-TL †; 36 G2: Waitlist; 10	12 weeks	45.2	38.4	96	NR	NR	Medium
Peterson et al., 1998 (47); United States	G1: CBT-TL ‡; 16 G2: CBT-PTL §; 19 G3: CBTssh ∥; 15 G4: Waitlist; 11	8 weeks	42.4	34.7	100	4	NR	Medium
Peterson et al., 2009 (48); United States	G1: CBT-TL ‡; 60 G2: CBT-PTL §; 63 G3: CBTssh ∥; 67 G4: Waitlist; 69	20 weeks	47.1	39	88	4	NR	Medium
Tasca et al., 2006 (44); Canada	G1: PIPT-TL ¶; 48 G2: CBT-TL **; 47 G3: Waitlist; 40	16 weeks	42.8	41.1	91	2	Mood disorder: 64.7	Medium
Pharmacologic interventions ($n = 11$)								
Arnold et al., 2002 (53); United States	G1: Fluoxetine, 80 mg/day; 30 G2: Placebo; 30	6 weeks	41.9 (9.7) 40.8 (9.0)	39.6 (7.0) 36.7 (6.8)	93 93	10 13	MDD: 25	Medium
Grilo et al., 2005 (54); United States	G1: Fluoxetine, 60 mg/day; 27 G2: Placebo; 27 G3: CBT + fluoxetine ††; 26 G4: CBT + placebo ††; 28	16 weeks	44	36.3	78	11	NR	Low
Guerdjikova et al., 2008 (58); 2008 (58); United States	G1: Escitalopram, 30 mg/day; 21 G2: Placebo; 23	12 weeks	39	40.2	96	27	NR	Low

Study, Year (Reference); Country	Intervention and Comparators; Randomly Assigned Participants, n	Treatment Duration	Mean Age (SD), y	Mean BMI (SD), kg/m^2	Female, %	Nonwhite, %	Current Axis I Diagnosis, %	Risk of Bias
Guerdjikova et al., 2012 (57); United States	G1: Duloxetine, flexible dose to max 120 mg/day; 20 G2: Placebo; 20	12 week	40.1	40.6	88	17		Low
Hudson et al., 1998 (59); United States	G1: Fluvoxamine, 300 mg/day; 42 G2: Placebo; 43	9 weeks	42	35.5	91	4	NR	Medium
McElroy et al., 2000 (60); United States	G1: Sertraline, 50 to 200 mg/day; 18 G2: Placebo; 16	6 weeks	42	36.1	94	NR	NR	Medium
McElroy et al., 2003 (56); United States	G1: Citalopram, 60 mg/day; 19 G2: Placebo; 19	6 weeks	40.6	37.8	95	13	Depression: 32	Low
McElroy et al., 2015 (49); United States	G1: Lisdexamfetamine dimesylate, 30 mg/day; 66 G2: Lisdexamfetamine dimesylate, 50 mg/day; 65 G3: Lisdexamfetamine dimesylate, 70 mg/day; 65 G4: Placebo; 64	11 weeks	39	34.9	82	22	NR	Medium
ClinicalTrials.gov, 2014 (50) and McElroy et al., 2016 (study 1) (52); United States, Germany, Sweden, and Spain	G1: Lisdexamfetamine dimesylate, 50 or 70 mg/day as tolerated to optimal clinical dose; 192 G2: Placebo; 191	12 weeks	38	33	87	22	NR	Low
ClinicalTrials.gov, 2015 (51) and McElroy et al., 2016 (study 2) (52); United States and Germany	G1: Lisdexamfetamine dimesylate, 50 or 70 mg/day as tolerated to optimal clinical dose; 195 G2: Placebo; 195	12 weeks	38	34	85	27	NR	Low
White and Grilo, 2013 (55); United States	G1: Bupropion, 300 mg/day; 31 G2: Placebo; 30	8 weeks	44.1	35.8	100	16	NR	Low
Trials not contributing to the (*n* = 20)								
Psychological interventions (*n* = 6)								
Carrard et al., 2011 (61); Switzerland	G1: CBTgsh##; 37 G2: Waitlist; 37	6 months	36	28.8	100	NR	NR	Medium

Study, Year (Reference); Country	Intervention and Comparators; Randomly Assigned Participants, n	Treatment Duration	Mean Age (SD), y	Mean BMI (SD), kg/m^2	Female, %	Nonwhite, %	Current Axis I Diagnosis, %	Risk of Bias
Carter and Fairburn, 1998 (62); United Kingdom	G1: CBTpsh§§; 24 G2: CBTgsh ‖‖; 24 G3: Waitlist; 24	12 weeks	39.7	31.6	100	3	NR	Medium
Tasca et al., 2012 (94) (follow-up to Tasca et al., 2006, [44]); Canada	G1: PIPT-TL¶; 48 G2: CBT-TL **; 47 G3: Waitlist; 40	16 weeks	42.8	41.1	91	2	Mood disorder: 64.7	Medium
Peterson et al., 2001 (95) (follow-up to Peterson et al., 1998 [47]); United States	G1: CBT-TL≠; 60 G2: CBT-PTL§; 63 G3: CBTssh //; 67 G4: Waitlist; 69	20 weeks	47.1	39	88	4	NR	Medium
Grilo et al., 2013 (96); United States	G1: CBTpsh + usual care¶¶; 24 G2: Usual care; 24	16 weeks	45.8	37.6	79.2	54.2	NR	Low
Masson et al., 2013 (97); Canada	G1: DBTgsh; 30 G2: Waitlist; 30	13 weeks	42.8 (10.5)	37.9	88.3	8.4	NR	Medium
Pharmacologic interventions (n = 8)								
Brownley et al., 2013 (98); United States	G1: Chromium, 1,000 µg/day; 8 G2: Chromium, 600 µg/day; 9 G3: Placebo; 7	6 months	36.6	34.2	83	12	NR	Medium
Guerdjikova et al., 2009 (99); United States	G1: Lamotrigine, mean dose 236 mg/day; 26 G2: Placebo; 25	16 weeks	44.5	40.1	76.5	80	Depressive disorders: 37.2	Medium
McElroy et al., 2011 (100); United States	G1: Acamprosate, 666 mg/day; 20 G2: Placebo; 20	10 weeks	46	39.5	85	12.5	NR	Medium
McElroy et al., 2013 (101); United States	G1: ALKS-33, 10 mg/day as tolerated; 32 G2: Placebo; 37	6 weeks	45.2	39	90	19	NR	Medium
McElroy et al., 2015 (102), USA	G1: Armodafinil, mean dose 216.7 mg/day; 30 G2: Placebo, mean dose 208.9 mg/day; 30	10 weeks	41.3	40.1	85	23	NR	Medium

Study, Year (Reference); Country	Intervention and Comparators; Randomly Assigned Participants, n	Treatment Duration	Mean Age (SD), y	Mean BMI (SD), kg/m^2	Female, %	Nonwhite, %	Current Axis I Diagnosis, %	Risk of Bias
McElroy et al., 2007 (103); United States	G1: Atomoxetine, mean dose 106 mg/day; 20 G2: Placebo; 20	10 weeks	41.1	39.3	82.5	15	Depressive disorders: 15	Medium
McElroy et al., 2003 (64); United States	G1: Topiramate, median dose 212 mg/day; 30 G2: Placebo, median dose 362 mg/day; 31	14 weeks	40.8	NR	87	NR	Mood disorder: 15	Medium
McElroy et al., 2007 (63); United States	G1: Topiramate, median dose 300 mg/day; 195 G2: Placebo, median dose 400 mg/day; 199	16 weeks	44.5	38.5	84.2	21.5	NR	Medium
Combination interventions (n = 6)								
Claudino et al., 2007 (104); Brazil	G1: CBT + topiramate, maximum dose 300 mg/day; 37 G2: CBT + placebo; 36	21 weeks	38.3	37.4	96	43	NR	Medium
Devlin et al., 2005 (105); United States	G1: BWL + CBT + fluoxetine, 60 mg/day; 28 G2: BWL + CBT + placebo; 25 G3: BWL + fluoxetine; 32 G4: BWL + placebo; 31	5 months	43	40.9	78	23	Major depression: 10.3	Medium
Golay et al., 2005 (106); Switzerland	G1: HC diet + orlistat, 120 mg 3 times/day; 44 G2: HC diet + placebo; 45	24 weeks	41	36.5	91	NR	NR	Low
Grilo, et al., 2005 (107); United States	G1: CBTgsh + orlistat, 120 mg 3 times/day; 25 G2: CBTgsh + placebo; 25	12 weeks	47	36	88	12	NR	Low
Grilo and White, 2013 (108); United States	G1: BWL + orlistat, 120 mg 3 times/day; 20 G2: BWL + placebo; 20	4 months	45.8	38.1	78	NR	NR	Low
Laederach-Hofmann et al., 1999 (109); Switzerland	G1: Individual diet counseling + group psychological support + imipramine: 25 mg 3 times/day; 15 G2: Individual diet counseling + group psychological support + placebo: same dosing as active treatment; 16	8 weeks	38.1	39.8	87	NR	NR	Medium

BED = binge-eating disorder; BMI = body mass index; BWL = behavioral weight loss; CBT = cognitive behavioral therapy; CBTgsh = cognitive behavioral therapy, guided self-help; CBTpsh = cognitive behavioral therapy, pure self-help; CBT-PTL = cognitive behavioral therapy, partially therapist-led; CBTssh = cognitive behavioral therapy, structured self-help; CBT-TL = cognitive behavioral therapy, therapist-led; DBTgsh = dialectical behavior therapy, guided self-help; G = group; HC = hypocaloric; MDD = major depressive disorder; NR = not reported; PIPT-TL = psychodynamic interpersonal psychotherapy, therapist-led.

*Fifteen 2-h manualized (93) group sessions in Dutch.

†Twelve 90-min manualized (110) group sessions.

‡Fourteen 60-min manualized (111) group sessions with 30-min therapist-led manualized psychoeducation and 30-min therapist-led discussion.

§Fourteen 60-min manualized (111) group sessions with 30-min manualized psychoeducation through videotape and 30-min therapist-led discussion.

//Fourteen 60-min manualized (111) group sessions with 30 min manualized psychoeducation through videotape and 30-min led by a group member assigned to facilitate group discussion.

¶Sixteen 90-min manualized (Tasca GA, Mikail S, Hewitt P. Group psychodynamic interpersonal psychotherapy: a manual for time limited treatment of binge eating disorder. Unpublished manuscript.) weekly group sessions.

**Sixteen 90-min manualized (Wilfley DE, Stein RI, Friedman MA, Beren SA, Wiseman CV. Group cognitive-behavioral therapy for binge eating disorder. Unpublished manuscript.) weekly group sessions.

††Sixteen weeks of individual, 60-min sessions using method of Fairburn et al. (112) plus 60 mg/day fluoxetine or placebo; CBT + fluoxetine gruop included in assessment of combination treatments.

‡‡Internet-guided; 11 sequential CBT modules + weekly e-mail contact with a coach; conducted in French; to be completed within 6 mo.

§§Individual provided with manual (113) and told to follow its self-help program independently.

////Individual provided with manual (113) plus support from nonspecialist therapists in six to eight 25-min sessions.

¶¶Participants were instructed to follow the advice and treatment recommendations of their primary care physician but received no specific intervention for BED.

Appendix Table 4

Harms Associated With Treatments for Binge-Eating Disorder: Qualitative Synthesis Results [*]

Harm and Intervention (Reference)	Trials, *n*	Participants, *n*	Events, *n*	Evidence and Events, *n*	Strength of Evidence
Headache					
amine (59)	1	85	70	Drug: 42 Placebo: 28	Insufficient for no difference
Topiramate (63, 64)	2	468	73	Drug: 37 Placebo: 36	Moderate for no difference
Sleep disturbance [*]					
Fluvoxamine (59, 114)	2	105	57	Drug: 42 Placebo: 15	Low for harm
Topiramate (63, 64)	2	468	89	Drug: 48 Placebo: 41	Moderate for no difference
Gastrointestinal upset					
Fluvoxamine (59, 114)	2	105	24	Drug: 18 Placebo: 6	Low for harm
Topiramate (63, 64)	2	468	94	Drug: 52 Placebo: 42	Moderate for no difference
Sympathetic nervous system arousal [†]					
Fluvoxamine (59, 114)	2	105	22	Drug: 15 Placebo: 7	Low for harm
Topiramate (63, 64)	2	468	243	Drug: 181 Placebo: 62	Moderate for harm
Decreased appetite					
Lisdexamfetamine[‡] (49, 52)	3	938	66	Drug: 53 Placebo: 13	Moderate for harm

[*] Insomnia plus other sleep disturbances (i.e., abnormal dreams, fatigue, sedation, somnolence, yawning).

[†] Includes anxiousness, dry mouth, feeling jittery, increased blood pressure, increased heart rate, palpitations.

[‡] Among participants randomly assigned to 50 or 70 mg/d.