Published in final edited form as:
Expert Opin Emerg Drugs. 2014 March ; 19(1): 99–142. doi:10.1517/14728214.2014.879291.

Current and Emerging Drug Treatments for Binge Eating Disorder

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Abstract

Introduction—This study evaluated controlled treatment studies of pharmacotherapy for binge eating disorder (BED).

Areas Covered—The primary focus of the review was on phase II and III controlled trials testing medications for BED. A total of 46 studies were considered and 26 were reviewed in detail. BED outcomes included binge-eating remission, binge-eating frequency, associated eating-disorder psychopathology, associated depression, and weight loss.

Expert Opinion—Data from controlled trials suggests that certain medications are superior to placebo for stopping binge-eating and for producing faster reductions in binge eating, and - to varying degrees - for reducing associated eating-disorder psychopathology, depression, and weight loss over the short-term. Almost no data exist regarding longer-term effects of medication for BED. Except for topiramate, which reduces both binge eating and weight, weight loss is minimal with medications tested for BED. Psychological interventions and the combination of medication with psychological interventions produce binge-eating outcomes that are superior to medication-only approaches. Combining medications with psychological interventions does not significantly enhance binge-eating outcomes, although the addition of certain medications enhances weight losses achieved with cognitive-behavioral therapy and behavioral weight loss, albeit modestly.

Keywords

binge eating; pharmacotherapy; medication; placebo; obesity

1. Background

Binge eating disorder (BED), one of three formal eating-disorder diagnoses in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*)[1], is defined

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Declaration of interest:
Deborah Reas declares no conflict of interest.
This review does not represent the views of the National Institute of Health. He serves as a consultant to Shire, serves on the editorial boards of professional journals, and has received author royalties from Guilford Press and Taylor and Francis Publishers for his academic books.

by recurrent binge eating (i.e., eating unusually large quantities of food accompanied by subjective feelings of loss of control), marked distress about the binge eating, and the absence of inappropriate weight compensatory behaviors (e.g., purging, laxative misuse, excessive exercise, or extreme restraint) that characterize bulimia nervosa. BED is a common clinical problem, with an estimated lifetime prevalence rate of roughly 2.8% in adults [2], and common in both sexes [2] and across minority groups [3]. BED is associated strongly with obesity [2] and is associated with elevated rates of medical [4] and psychiatric [5] co-morbidity. BED is frequently associated with increased depressive and body-image psychopathology [6] and with psychosocial impairment[2]. BED shares many features with, but is distinct from the other eating disorders and obesity [6–9].

2. Medical Need

Since BED was first introduced as a research category in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*)[10], the treatment literature has grown considerably for this eating disorder. BED represents a clinical challenge and effective treatments need to address binge eating, weight loss, and associated eating-disorder (e.g., body image concerns) and depressive psychopathology [11].

3. Existing treatment

Reviews have generally converged in suggesting that certain specialized psychological treatments, particularly cognitive behavior therapy (CBT) and interpersonal therapy (IPT) are effective for reducing binge eating and associated depressive and eating-disorder psychopathology but fail to produce weight loss [11;12]. Recent rigorous studies have found that behavioral weight loss (BWL) treatments are roughly comparable to CBT and IPT through 12-months post-treatment but have the specific advantage of also producing modest weight loss [13;14]. The effects of BWL, however, appear to be less durable than those for CBT and IPT [14] which seem robust through 48-months [15]. In contrast, the status of the literature on the effectiveness of medications for BED is less clear. Various reviews [16;17] and clinical guidelines[18;19] have suggested that certain medications have short-term efficacy for BED.

4. Market review

The clinical significance of the emerging pharmacotherapy literature requires careful interpretation due to mixed findings and methodological limitations and, to date, no specific medication has been approved for BED by the United States Food and Drug Administration.

5. Current research goals and 6. Scientific rationale

The goal of this review is to provide a critical overview of the controlled medication treatment literature for BED with a specific focus on phase II and phase III trials. This review updates and expands on our previous quantitatively-focused meta-analysis of pharmacotherapy for BED [17] by providing (1) updated coverage of new medications and developments in the field, (2) review of important clinical outcomes beyond just binge-

eating and weight-loss, and (3) offering "expert opinion" regarding the clinical implications for pharmacotherapy for BED.

7. Competitive environment

7.1. Search Strategy

This review aimed to systematically identify and synthesize existing evidence from Phase II and Phase III clinical trials for the use of pharmacological agents in the treatment of BED. Phase II trials for investigational new drugs were defined according to United States Food and Drug Administration standards as controlled clinical studies to evaluate the effectiveness of a drug and to determine the common short-term side effects and risks. Phase II studies are well-controlled and closely monitored, usually conducted in a relatively small number of patients of no more than several hundred subjects. Phase III clinical trials were defined as expanded controlled and uncontrolled trials, usually conducted with several hundred to several thousand patients, performed after initial evidence of effectiveness is documented, with the goal of collecting additional information about effectiveness and safety necessary for physician labeling and to evaluate the overall benefit-risk relationship.

Relevant studies were identified by searching the US National Institutes of Health Clinical Trials web-based registry of private and publicly-supported clinical studies as well as MEDLINE via PubMed, the Cochrane Library, and Google Scholar. Search terms included "binge eating" or "binge eating disorder" paired with terms "pharmacotherapy," "randomized controlled trials," "placebo-controlled," and further supplemented by direct searches for drug classes (e.g., "antiepileptics," "antidepressants") and individual medications (e.g., "topiramate," "sibutramine," "zonisamide"). Relevant studies were also identified by cross-referencing and manually-searching obesity, eating disorder, psychiatry, and pharmacology journals and article reference lists. Since BED was first introduced as a research category in the appendix of DSM-IV, literature published prior to 1985 offered little to no clinical data specific to the current definition of BED. Accordingly, we attempted to locate all Phase 2 and Phase 3 trials published between 1985 and October 1, 2013 or currently listed as "ongoing" in the NIH Clinical Trials database. Only randomized placebo-controlled trials or additive or combined trials evaluating the effects of a pharmacological agent as a primary treatment for BED were included.

Figure 1 illustrates the flow of the search strategy. Following the identification and screening of records, a total of 65 studies were assessed for eligibility. Phase I trials including open-label or case series (n=18) or retrospective cohort designs (n=1) were excluded. Of the remaining 46 potentially appropriate RCTs, a total of 20 trials were excluded. Previously published RCTs investigating d-fenfluramine [20], sibutramine [21], [22],[23;24], and rimonabant [25] and two ongoing clinical trials (NCT00829283 and NCT00537810) were not considered in the review because these medications were withdrawn from the market due to adverse events and safety concerns (n=8). Ongoing RCTs for armodafinil (NCT01010789) and methylphenidate (NCT01921582) or completed trials without study results for lisdexamfetamine/SPD489 (NCT01718509, NCT01718483, NCT01090713) were also excluded (n=5). Three early trials with uncertainty regarding BED diagnostic status, e.g., subclinical BED or non-purging BN [26–28] were excluded. A trial

from 1990 which collapsed non-binge eaters and binge-eaters in the main analyses was also excluded [29]. One trial investigating orlistat included in the clinical trials registry (NCT00601354) was excluded due to the very small sample size (n=9). Preliminary findings from conference proceedings presented at the 166th annual meeting of the American Psychiatric Association (May, 2013) were also excluded for two recently completed RCTs investigating opioid antagonist naloxone spray [30] and lisdexamfetamine dimesylate [31], as such preliminary data must be viewed cautiously until formal publications become available.

All eligible studies were examined for descriptive trial information and outcome data. Acceptability of treatment was measured by comparing and reporting data on attrition, i.e., the number of people per treatment group who dropped out for any reason. Primary outcome data included 1) the number of people per treatment group who achieved abstinence or remission (defined as 100% reduction in binge-eating episodes) and 2) decrease in the frequency of binge episodes or binge days. Available secondary outcomes were also examined, including 1) weight loss, 2) changes in eating psychopathology (e.g., disinhibition, restraint, craving) and 3) changes in associated or depressive psychopathology. For each study, this review provides an overview of the design and methods, including sample size, recruitment methods and diagnostic assessment, medication dosing and length of treatment, as well as information on study-defined efficacy and statistical analyses.

Table 1 lists a total of 46 trials, of which 26 were determined eligible for inclusion. Of these, a total of 17 were pharmacotherapy-only (16 testing placebo vs. drug and 1 testing drug vs drug) and 9 were additive/combination RCTs which investigated a pharmacological agent as a primary treatment for BED (using either placebo controls or other active treatment conditions. Three major classes of drugs were identified and these included antidepressants (of various modes of action), antiepileptics, and four diverse anti-obesity agents, three of which have been withdrawn from the market leaving orlistat as the sole anti-obesity that has been tested for BED. Lesser studied classes of drugs with completed or active RCTs included anti-craving/anti-addiction drugs (opiate blockers, glutamate antagonists), drugs for ADHD, GABA agonists, and drugs for excessive sleepiness.

8. Potential development issue

BED is associated strongly with obesity but many clinicians fail to identify the disordered eating in their obese patients. Obese persons with or without BED experience many forms of "anti-obesity" stigma and such negative experiences may adversely influence both treatment-seeking and doctor-patient relationships and compliance. Greater public and professional awareness of BED is needed. Another challenging potential development issue is that while obesity is universally recognized as a chronic physical issue requiring on-going intervention, the emerging pharmacotherapy literature for BED consists entirely of short-term trials testing "acute" treatment effects. The likely need for longer-term pharmacotherapy to address both eating and excess-weight needs in this specific patient group may represent a challenge to new medications that may have potential for abuse and dependence.

9. Conclusion

Tables 2 – 5 summarize the designs and specific findings from 26 RCTs testing pharmacotherapy for BED. Findings are presented below by different medication classes. The bulk of RCTs for BED reported to date have been performed by a relatively limited number of investigators at a few research sites. Nearly all of the RCTs were performed in the United States and were funded by the pharmaceutical industry (i.e., drug manufacturers). Nearly all RCTs used media recruitment methods for participants, have enrolled mostly women, and the studies were performed in research specialty clinics. The RCTs were typically very short duration, ranging from 6 to 24 weeks, testing only acute-treatment effects of medications on BED and very few follow-up data have been reported to date. Careful inspection of Tables 2–5 (columns 6–7) reveals that RCTs have varied considerably in their methods and rigor in both assessing and analyzing binge-eating outcomes.

9.1 Antidepressant Medications

Table 3 summarizes designs, methods, and findings from 14 controlled studies testing antidepressants of various modes of action for BED. Five RCTs, reported in 7 papers [32–38], tested monotherapy fluoxetine either against placebo [32;35] against monotherapy sertraline [37] against monotherapy fluvoxamine [38], against CBT, CBT plus fluoxetine, and CBT plus fluvoxamine [38], against CBT plus either placebo or fluoxetine[35]. Two RCTs, using additive/combination, tested whether fluoxetine was superior to placebo for enhancing CBT[35]or BWL[33] short-term outcomes. Fluoxetine was reported to be superior to placebo in one 6-week study [32] but not in a second 16-week study [35]; however, in the first study [32], although binge-eating reduced significantly faster with fluoxetine than placebo both end-point analyses and comparisons of binge-eating abstinence rates revealed non-significant differences. Fluoxetine did not differ significantly from two other SSRIs [37;38], that is, specifically from either sertraline [37] or from fluvoxamine [38]; the first study [37] did not include a placebo condition thus precluding comments about efficacy and the second study[38] found that both fluoxetine and fluvoxamine were significantly inferior to CBT alone or the CBT combined with each medication thus indicating lack of relative efficacy for monotherapy fluoxetine relative to other active treatments.

None of the additive/combination RCTs found that fluoxetine enhanced outcomes relative to placebo when combined with CBT[35] or behavioral weight loss [33] or relative to CBT alone[38]. The only three RCTs for BED that reported longer-term follow-up data reported lack of efficacy for both monotherapy fluoxetine [38] and fluvoxamine[38]and no additive effect relative to placebo when combined when either CBT [36]or with behavioral weight loss [34].

Two additional placebo-controlled RCTs of fluvoxamine reported that most outcomes did not differ significantly from placebo[39]. Hudson et al. (1998)[39] reported a significantly faster reduction rate in binge eating for fluvoxamine, no statistical advantage for binge-eating remission, and statistically significant but clinically-meaningless rate of weight loss (2.7 lbs vs 0.3 lbs). In a 6-week RCT, sertraline was associated with significantly greater reduction in binge-eating and weight loss, but not binge-eating remission or depression [40].

In a 6-week RCT, citalopram was associated with significantly faster reductions in binge-eating and depression but not in end-point analyses of binge-eating frequency, binge-eating remission, or depression, and statistical greater but clinically-meaningless weight loss than placebo [41]. Escitalopram did not differ significantly from placebo in binge-eating remission, binge-eating frequency, or depression, but had a statistically significant - albeit clinically-meaningless - weight loss (mean difference of 3.52 lbs) given that mean weights of participants was roughly 240 lbs [42].

Our qualitative summary of the available findings for SSRIs for BED, suggesting they have very limited efficacy, is consistent with a previous meta-analysis of seven available monotherapy SSRI placebo-controlled trials [17]. Specifically, the meta-analysis reported a statistically significant - but clinically minimal – relative risk (RR) value of 0.81 (95% CI: 0.70–0.94) for binge-eating remission and weighted mean difference (WMD) of –1.72 (95% CI = –3.06 – –0.37)[17].

Four additional RCTs have tested various antidepressants: two were monotherapy placebo-controlled RCTs testing duloxetine [43] and bupropion [44] and two were additive/combination RCTs testing imipramine versus placebo combined with diet and counseling[45] and desipramine as an added treatment following a sequenced approach involving CBT followed by behavioral weight loss [46]. Duloxetine was associated with significantly faster reduction in binge-eating than placebo but did not differ from placebo in binge-eating remission, end-point binge-eating frequency, depression, or weight loss [43]. Bupropion did not differ from placebo on binge-eating remission, binge-eating frequency, depression, or eating disorder psychopathology, but produced significantly greater – albeit minimal – weight loss (1.8% BMI loss vs 0.6% BMI loss) than placebo[44]. Combining imipramine with diet and counseling enhanced both binge-eating outcomes and weight loss outcomes [45] and adding desipramine during the last 6 months of a sequenced CBT-behavioral weight loss treatment did not enhance binge-eating outcomes but statistically significantly, albeit modestly, enhanced weight losses relative to conditions with desipramine [46].

9.2. Antiepileptic Medications

Table 4 summarizes designs, methods, and findings from five placebo-controlled RCTs testing antiepileptic medications for BED. Three placebo-controlled RCTs tested topiramate: two compared monotherapy topiramate versus placebo[47;48] and one tested whether topiramate was superior to placebo for enhancing CBT [49]. Topiramate was significantly superior to placebo in both RCTs [47;48] for producing binge-eating remission, faster rate of reductions in binge-eating frequency, and greater weight loss, but not for associated depression. The significant effects observed for topiramate, unlike those for antidepressant medications reviewed above, are clinically meaningful. Specifically, topiramate was associated with binge-eating remission rates of 64% (in intent-to-treat analyses) in the first RCT [47] and 58% (in "modified ITT" completer analyses) in the second and larger RCT [48]. Reas and Grilo [17] calculated significant RRs of 0.56 and 0.59, respectively, for achieving remission in the two studies, which indicate topiramate was associated with reduction of non-remission rates by 44% to 41%, respectively. Topiramate was also

associated with significant weight loss in both RCTs (means of 5.9 kg[47]and 4.5 kg[48]), making it the only available medication that has resulted in notable weight loss with BED. The addition of topiramate versus placebo to CBT did not significantly enhance the rate of reduction in binge-eating frequency, or reduce eating-disorder psychopathology or depression levels, but was associated with a significantly higher rate of binge-eating remission (defined based on one-week endpoint) and significantly greater weight loss (–6.8kg vs –0.9 kg)[49]. Such significant clinical outcomes, however, must be weighed against high rates of adverse events and dropout rates associated with topiramate which were 47% in one RCT [47] and 28% in the second RCT [48]. A longer-term open-label maintenance study of topiramate reported that 68% of patients discontinued taking topiramate which was associated with high rates of side effects and difficulties tolerating the medication [50]. Noteworthy is that attrition associated with topiramate was substantially lower (i.e., only 19%) when combined with CBT [49].

The two remaining RCTs of antiepileptics reported mixed findings[51;52] which were quite dampened relative to those reported in the topiramate RCTs. Zonisamide was significantly superior to placebo for producing a greater rate of reduction in binge-eating frequency and greater weight loss but not for producing binge-eating remission, end-point binge-eating frequency, or for reducing depression levels [52]. Lamotrigine was not superior to placebo for any measure of binge eating, associated eating-disorder pathology, depression, or for weight loss [51].

9.3. Anti-obesity Medications

There have been surprisingly few RCTs testing anti-obesity agents with BED especially given the strong association between BED and obesity. Table 1 lists all the anti-obesity agents that have been tested to date with BED. Three of the anti-obesity agents listed in Table 1 have been withdrawn from the market due to safety concerns and thus will not be reviewed here. We will note only that one of those anti-obesity medications – sibutramine – was found to be significantly superior to placebo for both reducing binge-eating and weight over the short-term in two RCTs [21;23]. Importantly, all of the RCTs that have anti-obesity agents for BED to date have employed “acute care” designs, i.e., they have been short-term in nature in sharp contrast to the treatment literature for obesity without BED which generally tests medications over 1–2 year periods.

A fourth anti-obesity agent – orlistat (a locally-acting medication that blocks fat absorption, without direct CNS effects) – was tested for BED in three placebo-controlled RCTs[53–55]. Table 5 summarizes the designs, methods, and findings from the three RCTs testing orlistat in diverse designs.

One RCT tested monotherapy versus placebo alongside a prescribed hypocaloric diet [53] and found that orlistat was associated with significantly great weight loss and reductions in eating-disorder psychopathology but did not differ from placebo for reducing binge eating or depression. Two placebo-controlled RCTs tested whether orlistat was superior to placebo for enhancing either CBT[54] or behavioral weight loss[55]. One RCT found that the addition of orlistat to CBT did not significantly enhance reductions in binge eating, eating-disorder psychopathology, or depression, but did significantly enhance weight loss outcomes relative

to placebo[54]. A second RCT found that the addition of orlistat to behavioral weight loss did not significantly enhance any outcomes (binge eating, eating-disorder psychopathology, depression, or weight loss) relative to placebo in obese patients with BED[55]. This later study [55], however, which randomized obese patients with versus without BED, found a significant moderator effect for BED status: the addition of orlistat to behavioral weight loss enhanced weight losses relative to placebo among obese patients without BED but not among obese patients with BED.

9.4. Other Medications

Table 5 summarizes designs and findings from RCTs testing several "other" medications. Two placebo-controlled RCTs have tested different "anti-craving or anti-addiction" medications and have published findings [56;57]. The two published RCTs testing anti-craving medications reported no significant advantage for either acamprosate [56] or for ALKS-33 [57] relative to placebo for any outcome measure, with the later medication resulting in 50% dropout rate.

One placebo-controlled RCT has published findings for ADHD medications [58]; one has reported preliminary-only findings at a conference [31] and others are still ongoing (Table 1). In a 10-week RCT with 40 patients, atomoxetine was reported to be significantly superior to placebo for achieving binge-eating remission, reducing binge-eating frequency, and for weight loss (albeit minimal) but not for reducing eating-disorder psychopathology or depression[58]. One other agent have been tested with a published report indicating chromium picolinate failed to show a significant advantage relative to placebo[59].

10. Expert Opinion

The evidence base regarding medications for BED is still in its early stages and remains limited. Since our last critical review of pharmacotherapy for BED[17] limited progress has occurred towards finding effective medications for patients with BED. Several more controlled trials have been published, two anti-obesity medications (sibutramine, rimonabant) have been withdrawn from the market due to safety concerns, and no specific medication has been approved for BED by the US FDA. Four additional controlled trials of new medications (methylphenidate, armodafinil, and 4 RCTs for lisdexamfetamine/SPD489) for BED have been completed but the findings have not yet been formally published and thus we could only review cautiously and preliminarily. Also noteworthy is that two new anti-obesity medications (phentermine/topiramate and lorcaserin) have been approved by the US FDA for the treatment of obesity but neither been tested for BED which seems like an important research avenue given the challenge of producing weight loss in this patient group.

Thus, while the evidence base regarding medications for BED continues to grow, it remains limited in the number of studies and specific medications tested. Even the medication-only studies with the best outcomes leave a substantial proportion (typically the majority) of patients without achieving abstinence from binge-eating and most report little weight loss. Moreover, in addition to the generally modest outcomes, most medication studies with BED are limited methodologically in several ways including relatively small sample sizes,

relatively brief durations, and limited generalizability due to potential clinic and recruitment biases, typical study eligibility criteria that exclude many BED patients, limited gender and racial/ethnic diversity that diverge from epidemiologic rates [55]. For example, much like the treatment literature for psychological treatments for BED [60] the overwhelming majority of participants in controlled trials testing medications have been white women. Most medication trials have had employed enrollment criteria that exclude many patients with common medical or psychiatric co-morbidities hence reducing generalizability. For example, the two largest medication trials to date[23;48] excluded patients with depression which is the most common co-occurring psychiatric disorder in BED[5]. Perhaps the greatest limitation of the medication treatment literature is the lack of follow-up findings. The lack of follow-up studies precludes any statements regarding optimal length of treatment, durability of the observed acute outcomes, and risk for and timing of relapse after medication discontinuation.

The expert opinion regarding current and emerging medications for BED is offered cautiously and within the context of the methodological limitations noted above. Available evidence from controlled trials suggests that certain medications are superior to placebo for helping patients to stop binge eating and for achieving faster reductions in binge eating. Certain medications are also superior to placebo, to varying degrees, for achieving improvements in patients with BED in associated areas such as reducing associated eating-disorder psychopathology and depression, and for producing weight loss over the short-term. Except for topiramate, which reduces both binge eating and weight, weight loss is unlikely to be substantial with available medications. Almost no data exist regarding the longer-term effects of medication for BED and the few available data suggest that relapse occurs following discontinuation. The issue of short-term treatment studies and lack of follow-up is especially critical for interpreting any medication's potential effect on weight loss and demands very cautious interpretation of any reported findings. Psychological interventions and the combination of medication with psychological interventions produce binge-eating outcomes that are superior to medication-only approaches over both short-term and longer-term follow-ups. Combining medications with psychological interventions does not significantly enhance binge-eating outcomes, although the addition of specific medications (topiramate and orlistat) enhances weight losses achieved with cognitive behavioral therapy and behavioral weight loss, albeit modestly.

The review concludes by offering implications for future research. Larger and longer studies with comprehensive assessment protocols for assessing changes in associated psychopathology and metabolic problems is clearly indicated. In addition to standard efficacy trials, there exists a need to perform treatment studies of medications with more diverse patient groups to increase generalizability. Larger studies with greater patient variability may also allow for the integration of analyses testing predictors and moderators of outcome[61]. The identification of significant predictors/moderators of response to specific medications might be a way to enhance pharmacotherapy outcomes via a more rational approach to prescription. Future studies such also include analyses of processes and treatment response. For example, Grilo et al (2006)[62] found that early rapid response to fluoxetine treatment was associated with positive outcomes in BED. Thus, although overall fluoxetine was not superior to placebo for treating BED[35], it appears that a subgroup of

patients who respond rapidly to fluoxetine go on to achieve good outcomes; this later finding echoes findings for antidepressant treatment response in bulimia nervosa[63] and depression[64]. Longer-term studies are needed to determine optimal treatment length as well as to inform questions about whether to discontinue medication and/or when to do so and in whom. For example, the medication treatment model for obesity clearly views weight control as a chronic or on-going treatment need. Finally, further research is needed using additive or combined approaches integrating specific psychological and medication treatments in order to enhance outcomes, particularly to enhance weight loss outcomes.

Acknowledgments

Carlos Grilo was supported during the preparation of this review by grants from the National Institute of Health (R01 DK49587, R01 DK073542, and K24 DK070052) although no additional funding was received for completion of this work.

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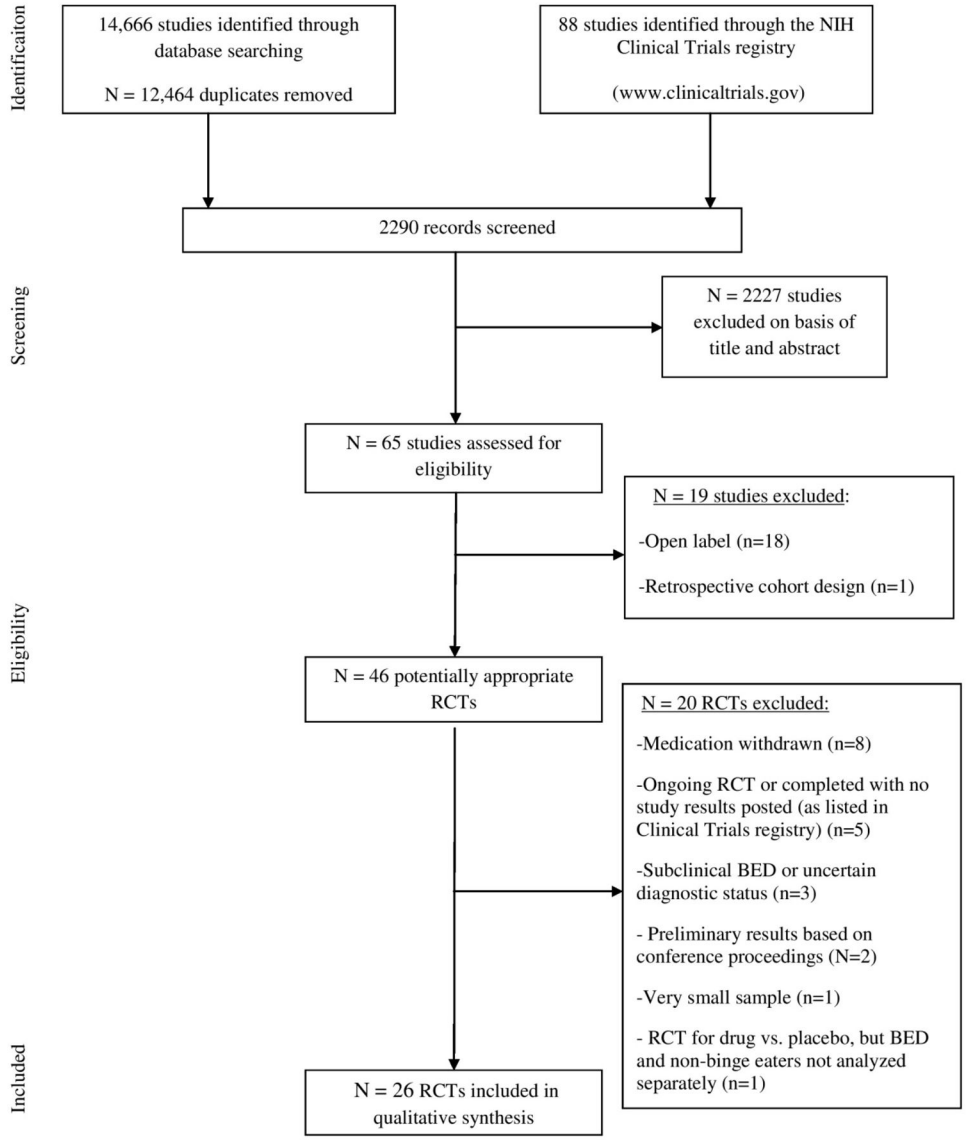


Figure 1.
Flow of the search strategy

Expert Opin Emerg Drugs. Author manuscript; available in PMC 2015 March 01.

Table 1

Summary of All Potentially Appropriate Randomized Controlled Drug Trials for Binge Eating Disorder (N=46)

Class	Drugs	No. of RCTs [a,b]	Studies
Antidepressants	**SSRI**		
	Fluoxetine	3[a],, 4[b]	Arnold et al. (2002)[32], Devlin et al. (2005, 2007)[33;34], Greeno & Wing (1996)[29][c], Grilo et al. (2005, 2012)[35;36], Leombruni et al. (2008)[37], Marcus et al. (1990)[27][d], Ricca et al. (2001)[38]
	Fluvoxamine	2[a], 1[b]	Hudson et al. (1998)[39], Pearlstein et al. (2003)[65], Ricca et al. (2001)[38]
	Sertraline	2[a]	Leombruni et al. (2008)[37], McElroy et al. (2000)[40]
	Citalopram	1	McElroy et al. (2003)[41]
	Escitalopram	1	Guerdjikova et al. (2008)[42]
	SNRI		
	Duloxetine	1	Guerdjikova et al. (2012)[43]
	Tricyclics		
	Desipramine	2[b]	Agras et al. (1994)[46], McCann & Agras (1990)[28][d]
	Imipramine	1[b]	Laederach-Hofmann et al. (1999)[45]
	Aminoketones		
	Buproprion	1	White and Grilo (2013)[44]
Antiepileptics	Topiramate	2[a], 1[b]	Claudino et al. (2007)[49], McElroy et al. (2003)[47], McElroy et al. (2007)[48]
	Zonisamide	1	McElroy et al. (2006)[52]
	Lamotrigine	1	Guerdjikova et al. (2009)[51]
Anti-obesity agents	Sibutramine	3[a]3[b]	Appolinario et al. (2003)[21][e], Bauer et al. (2006)[24][d, e], Milano et al. (2005)[22][e], Wilfley et al. (2008)[23][e], ongoing clinical trials #NCT00829283[e] and #NCT00537810[e]
	Orlistat	4[b]	Golay et al. (2005)[53], Grilo et al. (2005)[54], Grilo & White (2013)[55], #NCT00601354[f]
	D-fenfluramine (DXF)	1	Stunkard et al. (1996)[20][e]
	Rimonabant	1	Pataky et al. (2013)[25][d,e]
Anti-craving/Anti-addiction drugs	ALKS-33	1	McElroy et al. (2013)[57]
	Acamprosate	1	McElroy et al. (2011)[56]
	Naloxone	1	Preliminary findings reported by Alho et al. (2013)[30][g]

Class	Drugs	No. of RCTs [a,b]	Studies
Drugs for ADHD	Atomoxetine	1	McElroy et al. (2007)[58]
	Lisdexamfetamine/SPD489	4	Preliminary findings reported by McElroy et al. (2013)[31][g]. Ongoing or completed RCTs with no study results: #NCT01718509[h], #NCT01718483[h], #NCT01090713[h]
	Methylphenidate	1[b]	Ongoing clinical trial #NCT01921582[h]
Other agents	Baclofen	1	Corwin et al. (2012)[26][d,f]
	Chromium Picolinate	1	Brownley et al. (2013)[59]
	Armodafinil	1	Ongoing clinical trial #NCT01010789[h]

Note. The studies by Ricca et al. [38] and Leombruni [37] included arms to investigate two drugs, thus appearing twice in the table, but these studies are each considered only one unique RCT. Studies by Grilo[35;36] and Devlin [33;34] had separately published follow-up studies, but each are considered one unique RCT. SSRI = selective serotonin reuptake inhibitor. SNRI = serotonin–norepinephrine reuptake inhibitor.

[a] Pharmacotherapy-only RCT.

[b] Additive/combination therapy.

[c] Excluded due to grouping non-binge eaters and BED in analyses.

[d] Excluded due to uncertain BED diagnosis due to assessment limitations.

[e] Excluded due to withdrawn drug from market due to safety concerns.

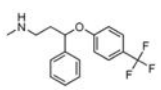
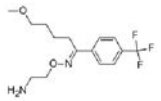
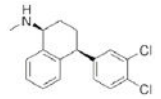
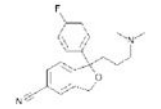
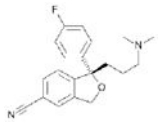
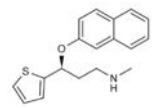
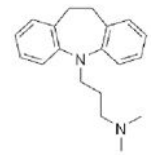
[f] Excluded due to very small sample size.

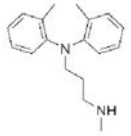
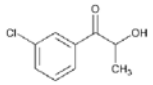
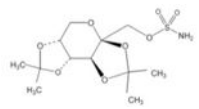
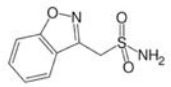
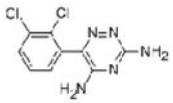
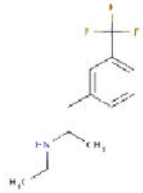
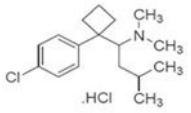
[g] Excluded due to preliminary data only based on conference proceedings.

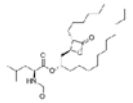
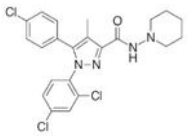
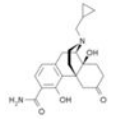
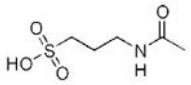
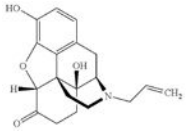
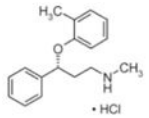
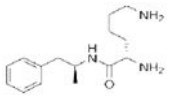
[h] Excluded due to ongoing RCT or completed but no study results posted.

Table 2

Competitive environment table

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Fluoxetine	Eli Lilly		MDD, OCD, BN, PMDD, panic disorder	Phase II	5-HT uptake inhibitor
Fluvoxamine	Abbott		Depression, OCD, panic disorder, social anxiety disorder	Phase II	5-HT uptake inhibitor
Sertraline	Pfizer		MDD, OCD, panic disorder, PTSD, PMDD, social anxiety disorder	Phase II	5-HT uptake inhibitor
Citalopram	Lundbeck		MDD, OCD, panic disorder	Phase II	5-HT uptake inhibitor
Escitalopram	Lundbeck		MDD, panic disorder, GAD, social anxiety disorder, OCD	Phase II	5-HT uptake inhibitor
Duloxetine	Eli Lilly		MDD, GAD, fibromyalgia, incontinence	Phase II	5-HT uptake inhibitor, adrenergic transmitter uptake inhibitor, serotonin and norepinephrine reuptake inhibitor
Imipramine	Sinclair IS Pharma		Depression	Phase II	Tricyclic antidepressant, 5-HT uptake inhibitor, adrenergic transmitter uptake inhibitor, serotonin and norepinephrine reuptake inhibitor

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Desipramine	Novartis		Depression	Phase II	Tricyclic antidepressant, 5-HT uptake inhibitor, adrenergic transmitter uptake inhibitor, serotonin & norepinephrine reuptake inhibitor
Buproprion	GlaxoSmith Kline		Depression, smoking cessation	Phase II	Dopamine reuptake inhibitor, adrenergic transmitter uptake inhibitor, norepinephrine/ dopamine dual reuptake inhibitor
Topiramate	Johnsen & Johnsen		Epilepsy, Lennox-Gastaut syndrome, Migraine prophylaxis	Phase II	GABA A receptor agonist, anhydrase inhibitor, AMPA receptor antagonist, kainate receptor antagonist, voltage- gated sodium channel antagonist
Zonisamide	Dainippon Sumitomo Pharma		Epilepsy, Parkinson's disease	Phase II	GABA receptor agonist
Lamotrigine	GlaxoSmith Kline		Epilepsy, depression (bipolar), psychosis (bipolar)	Phase II	Voltage-gated sodium channel antagonist
D-fenfluramine	Servier		Anti-obesity	Withdrawn	5-HT uptake inhibitor and 5-HT releaser
Sibutramine	Abbott (formerly Knoll)		Anti-obesity	Withdrawn	5-HT uptake inhibitor, adrenergic transmitter uptake inhibitor, serotonin-norepinephrine-dopamine reuptake inhibitor

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Orlistat	Hoffmann-La Roche		Anti-obesity, Type II diabetes	Phase II	Lipase inhibitor
Rimonabant	Sanofi		Anti-obesity	Withdrawn	Inverse agonist for the cannabinoid receptor CB1
ALKS-33	Alkermes		Addiction	Phase II	Opioid mu receptor antagonist Partial delta/ kappa receptor antagonist/agonist
Acamprosate	Merck		Addiction, alcohol	Phase II	Excitatory amino acid receptor, antagonist GABA receptor agonist, NMDA antagonist
Naloxone Spray	Lightlake Therapeutics		Addiction	Phase II	Opioid receptor antagonist
Atomoxetine	Eli Lilly		ADHD	Phase II	Adrenergic transmitter uptake inhibitor
Lisdexamfetamine/SPD489	Shire		ADHD	Phase III	Adrenoreceptor agonist, alpha adrenoreceptor agonist, dopamine reuptake inhibitor, adrenergic transmitter uptake inhibitor

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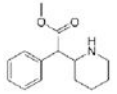
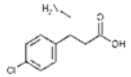
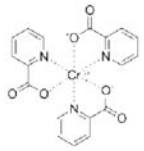
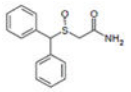
Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Methylphenidate	Novartis		ADHD	Phase II	Dopamine-norepinephrine reuptake inhibitor
Baclofen	IMPAX Laboratories		Muscular sclerosis, spasticity	Phase II	GABA-B receptor agonist
Chromium Picolinate	Nutrition21, Inc.		Chromium deficiency	Phase II	Dietary supplement
Armodafinil	Teva (formerly Cephalon)		Narcolepsy, sleep apnea	Phase III	Alpha 1 adrenoreceptor agonist

Source: Pharmaprojects (Citeline, 2013 Informa UK Ltd.)

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Table 3

Randomized Controlled Trials of Antidepressants (SSRI, SNRI, Tricyclics, Aminoketone) for Binge Eating Disorder

Study	Sample	Intervention	Trial Length	Recruitment/Diagnostic assessment	Study efficacy	Findings
Arnold et al. (2002)[32]	N=60 93% female Mean age 41.9 (drug) 40.8 (placebo) Mean BMI: 39.6 (drug) 36.7 (placebo)	Drug class: SSRI 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 wks	Country: USA Single-site Recruitment via media SCID-I/P interview to assess DSM-IV criteria and patients also had ≥ 3 OBE weekly for 6 months.	Primary measure of efficacy was frequency of binge eating episodes. Mixed-model repeated measures comparing rate of change between groups (time-by-treatment interaction was measure of effect). ITT and completer endpoint analyses, and exact trend test for response categories.	Attrition A total of 24/60 (40%) dropped out of treatment, 23% (n= 7 of 30) from the drug condition and 57% (n= 17 of 30) from the placebo condition (p=.02). Binge Eating OBEs per week decreased from 6.0 to 1.8 in the drug condition and 6.1 to 2.7 in the placebo condition indicating a faster rate of reduction for fluoxetine (p =.03). Endpoint analyses showed no difference in binge frequency between groups (p=.22) 45% in the drug condition versus 23.8% in the placebo condition were abstinent from binge eating (ns). Weight Loss Mean weight loss was 3.9 kg in the drug condition versus a gain of 0.7 kg in the placebo condition and this difference was significant in the time trend and endpoint analyses. Depression/Associated Psychopathology CGS-S scores improved at a greater rate for fluoxetine (p=.03). A trend was observed for a greater rate of reduction for HAM-D scores in fluoxetine group (p=0.06).
Devlin et al (2005) [33;34]	N=116 78% female Mean age: 43yrs Mean weight: 115.0 kg N=114/116 were included at 2-yr FUP	Drug class: SSRI Design: Additive Placebo-controlled, double-blind RCT (2 by 2 balanced factorial design) comparing **fluoxetine** vs. placebo versus CBT + **fluoxetine** vs. CBT + placebo all given in addition to behavioral weight loss (BWL). 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 below 60mg/day if needed to manage side- effects.	20 wks 24-mo	Country: USA Single-site trial Recruitment via media BED diagnosis established with the EDE-interview (12.0) and additional items from DSM-IV Appendix B. SCID interview assessed comorbid Axis I disorders	Linear regression models (main effects and time-by-treatment interaction)	Attrition A total of 42/116 (36%) dropped out of treatment. 32% of CBT versus 40% not receiving CBT dropped out (n.s.). 28% receiving fluoxetine versus 45% receiving placebo dropped out (p = .07). At FUP, 74/116 (64%) patients from acute treatment attended at least one maintenance group; of these, mean number of sessions attended = 11.3. Binge Eating and Weight Loss At post-treatment, the addition of CBT to BWL significantly enhanced reduction in binge eating frequency (p<.001) and binge remission rates (62% vs 33%; p<.001) relative to BWL without CBT. The addition of fluoxetine to BWL did not significantly improve remission rates (52% vs 41%), or weight loss relative to BWL with placebo. At FUP, the addition of CBT, but not the addition of fluoxetine to BWL resulted in significantly greater reductions in binge eating and remission.

Study	Sample	Intervention	Trial Length	Recruitment/Diagnostic assessment	Study efficacy	Findings
		Following initial 5-month acute treatment with **fluoxetine**, a 2-year maintenance phase was offered. Maintenance treatment included double blind medication for 18/24 months and monthly behavioral weight control groups.	Following initial 5-month acute treatment with placebo	Following initial 5-month acute treatment with		At post-treatment, there were no significant main effects for either CBT assignment or medication assignment on weight loss. No significant changes in weight were observed during the 24-month FUP. Depression/Associated Psychopathology At post-tx, there were no significant group interaction effects for the BSQ or TFEQ. At FUP, fluoxetine demonstrated a marginal advantage on BSQ and a CBT- by-time interaction was found, with continuing improvements. At post-tx, fluoxetine was associated with improvement on BDI vs. placebo and this held at FUP. At FUP, the combo treatment was associated with improvement in depression compared to CBT, fluoxetine- only, or placebo-only.
Grilo et al. (2005, 2012) [35;36]	N=108 78% female Mean age: 44 yrs Mean BMI: 36.3 kg/m^2	Drug class: SSRI Design: Additive Placebo-controlled, double-blind RCT (2 by 2 balanced factorial design) comparing **fluoxetine** vs. placebo versus CBT + **fluoxetine** vs. CBT + placebo. Fixed dosage of 60 mg/ day. CBT delivered in 16 one-hour individual weekly sessions following manualized protocol.	16 wks 6-month and 12-month FUP	Country: USA Single-site trial Recruitment via media SCID-I/P to establish DSM-IV BED, confirmed with EDE-interview	Primary outcome was remission (defined as zero OBE during past 28 days) analyzed with ITT chi- squares using baseline observations carried forward for missing data. Mixed-effects regression models were performed for continuous variables (OBEs, BMI, BDI, EDE- Q), with time-by- treatment interaction and post-hoc comparisons at post-tx, 6-mo, and 12-mo FUP.	Attrition A total of 22/108 (20%) dropped out of treatment. A total of 58/81 (72%) participated in the 12-month FUP. Binge Eating At post-treatment, 22% in fluoxetine-only, 26% in placebo, 50% in CBT + fluoxetine and 61% in CBT + placebo achieved remission. At 6-month FUP, 3.7% in fluoxetine-only, 34.6% for CBT + fluoxetine and 25% for CBT + placebo achieved remission (p =.018). CBT + fluoxetine and CBT + placebo did not differ from each other, but both differed from fluoxetine-only. At 12-month FUP, 3.7% in fluoxetine-only, 26.9% in CBT + fluoxetine, and 35.7% in CBT + placebo group achieved remission (p=.012). CBT + fluoxetine and CBT + placebo did not differ from each other, but both differed from fluoxetine-only. Weight Loss At post-treatment and 12-month FUP, weight loss was modest and did not differ between any of the groups. Depression/Associated Psychopathology At post-treatment, CBT + placebo and CBT + fluoxetine did not differ significantly on any secondary measures (EDE-Q, BSQ, TFEQ, BDI). However, both CBT groups demonstrated a significant advantage over fluoxetine-only and placebo-only. At 12-mo FUP, CBT + placebo and CBT + fluoxetine showed a significant advantage over fluoxetine-only for nearly all secondary outcomes, but did not significantly differ from

Study	Sample	Intervention	Trial Length	Recruitment/Diagnostic assessment	Study efficacy	Findings
						each other, indicating the effectiveness of CBT but not fluoxetine.
each other, indicating the effectiveness of CBT but not fluoxetine.
Leombruni et al. (2008) [37]	N=42 100% female Mean age: 39.6 Mean BMI: 40.2 (fluoxetine) 38.6 (sertraline)	Drug class: SSRI Double-blind RCT comparing **fluoxetine vs. sertraline** Start dosage of **fluoxetine** = 10 mg/day. Increased to 80 mg/day, as tolerated. End dosage mean = 64.5 (9.9) mg/day Start dosage of **sertraline** = 25 mg/day. Increased to 200 mg/day, as tolerated. End dosage mean = 165.9 (32.3) mg/day	24 wks	Country: Italy Single-site trial Treatment- seeking women at a university clinic DSM-IV-TR criteria establish by SID-OP	GLM and repeated measures ANOVA across 4 timepoints (baseline, 2, 3, and 6 months) and time-by- treatment interaction. Bonferroni posthoc comparisons used. Primary outcome variables were weight loss (5% loss defined response), binge frequency, and BES (< 17 defined response on BES) and BDI. Completer analyses.	Attrition A total of 5/20 (25%) in the fluoxetine group dropped out of treatment and 6/20 (27%) in the sertraline group dropped out (ns). Binge Eating 53% of the fluoxetine group and 60% of the sertraline group achieved abstinence from binge eating at week 24 (two drugs did not differ significantly). Approximately 50% of both groups achieved a response per study definition of < 17 BES cut-off. Weight Loss Mean BMI decreased from 40.2 to 38.5 in the fluoxetine group and from 38.6 to 36.6 in the sertraline group (two drugs did not differ significantly). Approximately 50% of both groups achieved a 5% weight loss. Depression/Associated Psychopathology CGI and BDI scores improved significantly for both groups, but no significant differences were detected between groups.
Ricca et al (2001) [38]	N=108 59% female Mean age: 25.9 yrs Mean BMI: 32.3	Design: Additive Controlled parallel-series open-label study compared five treatment conditions: CBT; CBT +**fluoxetine**; CBT +**fluvoxamine; fluoxetine-only; fluvoxamine-only.** CBT delivered via 22 individual 50-minute sessions. Fluoxetine dosing as follows: 20 mg/day first week, g/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 ti.d. for following 20 weeks; monthly medication visits.	24 wks 12-mo FUP	Country: Italy Two-site study Recruitment via two outpatient clinics DSM-IV criteria assessed by face- to-face interview; EDE (v. 12.0) defined binge frequency (OBE/28 days) administered SCID for DSM-III-R assessed comorbid Axis I disorders.	ITT endpoint analyses and completer analyses.	Attrition Attrition rates as follows: 15% for CBT; 27% for CBT+ fluoxetine, 22% for CBT +fluvoxamine, 24% for fluoxetine- only and 27% for fluvoxamine-only. 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<.001) but not in the fluoxetine-only or the fluvoxamine-only groups. 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 among completers. BMI loss for CBT, CBT+fluoxetine, and CBT-fluvoxamine did not differ significantly. Depression/Associated Psychopathology EDE scores improved significantly at post-treatment for the CBT, CBT+fluoxetine, and CBT+fluvoxamine groups, with the exception of the restraint score in the CBT-FLX group. No significant reduction in EDE scores were observed in the fluoxetine and fluvoxamine-only groups at post-treatment or FUP. Depression (BDI) scores were significantly reduced at the end of treatment in all groups at post-tx and at 1-year FUP, but no group differences detected.

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Study	Sample	Intervention	Trial Length	Recruitment/Diagnostic assessment	Study efficacy	Findings
Hudson et al. (1998)[39]	N=85 90.5% female Mean age: 41.2 (drug) 43.0 (placebo) Mean BMI: 34.2 (drug) 36.8 (placebo)	Drug class: SSRI 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 wks	Country: USA Multi-site trial Recruitment via media SCID for DSM-III-R interview; DSM-IV criteria (Note: patients reported 3 OBE per week for 6 mos as well as 2 days/wk for 6 mos)	Primary outcome were frequency of binges and CGI scores. Repeated measures random regression analyses comparing rate of change between groups (treatment-by- time interaction determined measure of effect). Response categories presented were: completer, evaluable-subjects, and ITT analyses (LOCF).	Attrition A total of 18/85 (21%) dropped out of treatment, 31% (n= 13 of 42) from the drug condition and 12% (n= 5 of 43) from the placebo condition. Binge Eating At baseline, OBE/week was 5.4 (2.9) in the drug condition and 5.3 (2.5) in the placebo condition. Rate of reduction in OBE frequency was reported significant (p <.001). In the ITT group, 38% in the drug condition versus 26% in the placebo condition achieved remission (ns). Weight Loss Estimated mean weight loss was 2.7 lbs in the drug condition versus 0.3 lbs for placebo for a 65-inch tall subject. Rate of change significantly greater for fluvoxamine (p=.04). ED Psychopathology N/A Depression/General Psychopathology No significant difference between placebo and fluvoxamine in the rate of decrease in depression (HAM-D). Fluvoxamine was associated with a greater rate of reduction in CGI severity scores.
Pearlstein et al. (2003) [65]	N=25 85% female Mean age: 41 yrs Mean BMI: 41.2 yrs	Drug class: SSRI Placebo-controlled, double-blind, forced titration, flexible-dose RCT of **fluvoxamine**. End dosage = 239 mg/day	12 wks	Country: USA Single-site trial Recruitment via media and clinical referrals EDE (v. 12) interview (adapted to meet DSM-IV criteria). SCID for DSM-IV administered at 2nd intake assessment.	Primary outcome variable inc. OBE frequency (EDE). Repeated measures ANOVAs (time-by-treatment interaction).	Attrition A total of 5/20 (25%) dropped out of treatment. Attrition was not reported separately for medication and placebo. Binge Eating Among completers, over 50% of both groups reported abstinence. Binge days in the past 28 days decreased from 14.7 to 3.1 in the drug condition vs 20.0 to 7.3 for placebo (ns). Weight Loss Mean weight decreased from 243 to 242 lbs for the drug condition vs. increased from 258 to 262 lbs for placebo (ns). Depression/General Psychopathology No significant between-group differences existed for any treatment outcome variable (BDI, CGI, HAM-D, SCL-90).
McElroy et al. (2000) [40]	N=34 94% female Mean age: 43.1 (drug) 41.0 (placebo) Mean BMI: 36.4 (drug) 35.8 (placebo)	Drug class: SSRI 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 wks	Country: USA Single-site trial Recruitment via media SCID interview to establish BED according to DSM-IV criteria. Patients also had 3 OBE weekly for at least 6 months.	Repeated measures random regression analyses for continuous data comparing rate of change. Primary outcome was reduction in mean number of binges/wk. ITT analyses used but completer data	Attrition A total of 8/34 (24%) dropped out of treatment, 28% (n= 5 of 18) from the drug condition and 19% (n= 3 of 16) from placebo. Binge Eating OBEs per week decreased from 7.6 to 1.1 in the drug condition and 7.2 to 3.9 in the placebo condition (p<.01). Rate of change in binge frequency was greater for sertraline than placebo. Among completers, 7/13 (54%) in the drug condition versus 2/13 (15%) in the placebo

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Study	Sample	Intervention	Trial Length	Recruitment/Diagnostic assessment	Study efficacy	Findings
					reported for response category reported for response category)	condition reached abstinence (p=.06, exact trend test). Weight Loss Estimated mean weight loss for a 65 inch subject was 12.3 lbs for the drug condition versus 5.3 lbs for the placebo condition (p<.01). Rate of decrease in BMI was significantly greater in sertraline group than placebo. Depression/General Psychopathology No significant between-group difference existed for depression (HAM-D). Sertraline was associated with a greater rate of reduction in CGI severity scores.
McElroy et al. (2003) [41]	N=38 95% female Mean age 42.0 (drug) 39.2 (placebo) Mean BMI: 41.4 (drug) 34.2 (placebo)	Drug class: SSRI 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 wks	Country: USA Single-site trial Recruitment via media SCID interview for DSM-IV Axis I disorders (Research Version)	Primary measure of efficacy was frequency of binge eating episodes. Mixed-model repeated measures comparing rate of change between groups (time-by-treatment interaction was measure of effect). ITT endpoint analyses, and exact trend test for response categories.	Attrition A total of 7/38 (18%) dropped out of treatment, 16% (n= 3 of 19) from the drug condition and 21% (n= 4 of 19) from the placebo condition. Binge Eating OBEs per week decreased from 5.2 to 1.7 in the drug condition and 5.7 to 3.4 in the placebo condition, which indicated a significantly greater rate of reduction for the citalopram group. Endpoint analyses showed no significant group difference for binge episodes (p=.09). A total of 47% in the drug condition versus 21% in the placebo condition achieved remission (p=.07). Weight Loss Mean BMI decreased from 41.1 to 40.9 in the drug condition versus an increase from 34.2 to 35.7 in the placebo condition, which indicated a significantly greater advantage for the citalopram group (p<.001). Depression/General Psychopathology A marginally significant difference in rate of change existed for depression (HAM-D, p=.05). Citalopram was associated with a significantly greater rate of reduction in obsessions and compulsions (YBOCS-BE) and CGI severity ratings. Endpoint analyses found no significant differences for HAM-D (p=.10) or CGI-S (p=.29).
Guerdjikova et al. (2008) [42]	N=44 97.7% female Mean age: 36.9 (drug) 41.0 (placebo) Mean weight: 40.1 (drug) 40.3 (placebo)	Drug class: SSRI 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 wks	Country: USA Single-site Recruitment via media SCID for DSM-IV	Longitudinal analyses comparing rate of change of weekly binge frequency during treatment between groups (binge episodes per week) estimated by random regression methods	Attrition A total of 10/44 (22.7%) dropped out of treatment, 25% (n= 5 of 20) from the drug condition and 17.3% (n= 4 of 23) from the placebo condition. Binge Eating OBEs per week decreased from 4.9 (2.6) to 0.9 (1.4) in the drug condition and from 5.1 (2.3) to 1.7 (1.5) in the placebo condition. No significant group differences were found in rate of improvement, but endpoint analyses indicated

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Study	Sample	Intervention	Trial Length	Recruitment/Diagnostic assessment	Study efficacy	Findings
					model (treatment by time interaction) model (treatment by time interaction). Secondary endpoint analyses included ITT (LOCF) analyses.	significant advantage to duloxetine for binge frequency (p=.04) A total of 50% in the drug condition versus 26% in the placebo condition reached abstinence (n.s.). Weight Loss Mean weight loss was 1.0 (2.6) kg in the drug condition versus a weight gain of 0.6 kg (2.4) kg for placebo (p<.001). Duloxetine showed a significant advantage in the rate of improvement for weight and BMI. Depression/Associated Psychopathology No significant differences existed between groups for depression (HAM/D) or obsessions and compulsions (YBOCS-BE) in rate of improvement. Escitalopram was associated with a greater rate of improvement for CGI-Severity scores.
Guerdjikova et al. (2012) [43]	N= 40 88% female Mean age: 44.4 (drug) 35.7 (placebo) Mean BMI: 38.7 (drug) 42.8 (placebo)	Drug class: SNRI Placebo-controlled, double-blind RCT of **duloxetine** Start dosage = mean 30 mg/ day Mean final dosage = 78.7 mg/day	12 wks	Country: USA Single-site trial Recruitment via media Patients met DSM-IV criteria (SCID- I/ P)for both BED and a current depressive disorder	Longitudinal analyses comparing rate of change of weekly binge frequency during treatment between groups (binge days per week) estimated by random regression methods model (treatment by time interaction). Secondary endpoint analyses included ITT (LOCF) analyses.	Attrition A total of 13/40 (32.5%) dropped out of treatment, 35% (n= 7 of 20) from the drug condition and 30% (n= 6 of 20) from the placebo condition. Binge Eating Binge days decreased from 4.0 (1.8) to 1.0 (1.7) in the drug condition and 3.5 (1.5) to 1.3 (1.2) in the placebo condition. This was a non-significant endpoint in the ITT analysis with LOCF, but p =.02 in longitudinal analysis comparing rate of change. 56% in the drug condition versus 30% in the placebo condition were abstinent from binge eating (p = .09). Weight Loss Mean BMI decreased from 38.7 (6.8) to 37.7 (7.5) for the drug condition vs. 42.8 (7.6) to 42.9 (7.3) for placebo (n.s.). Wt loss (kg) was 3.2 (6.4) in the drug condition and 0.30 (2.2) kg in the placebo condition (p=.04 in longitudinal and p =.07 endpoint analyses). Depression/Associated Psychopathology There were no significant differences between groups on secondary measures (TFEQ, YBOCS, Hamilton Anxiety Scale) but some advantage to duloxetine was observed on CGI-severity of illness scale for depressive disorders in rate of change.
Laederach-Hofmann et al. (1999) [45]	N=31 87% female Mean age: 40.7 (drug) 35.7 (placebo) Mean weight (kg):	Drug class: Tricyclics Design: Additive Placebo-controlled double-blind RCT comparing **imipramine** versus placebo in combination with diet	8 wks 6-mo open-phase FUP (no drug but dieting/ counseling continued).	Country: Switzerland Single-site trial Recruitment at a medical outpatient clinic. Existing medical charts reviewed and suitable patients invited to participate. DSM-IV criteria (inc. criteria A and C)	Repeated measures ANOVA with Bonferroni/D unn corrections and post-hoc Fisher PLSD t-test comparisons.	Attrition A total of 2/31 (6%) dropped out of treatment (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 to 2.5 to 4.1

Study	Sample	Intervention	Trial Length	Recruitment/Diagnostic assessment	Study efficacy	Findings
	96.0 (drug) 114.8 (placebo)	counseling with psychological support. Fixed dosage of 25 mg three times daily. Bi-weekly (30 min) diet counseling plus bi-weekly (15–25 min) psychological supportive therapy plus three 1–1.5 hour behavioral group therapy sessions.				binges/wk at post-tx and FUP, respectively for imipramine versus 7.1 to 5.3 to 7.2 binges/wk at post-tx and FUP, respectively for placebo; p. 238 data) with significant group differences detected at both timepoints ($p < .02$ at 8 weeks, $p<.001$ at 6-months FUP). Weight Loss The addition of imipramine resulted in significantly more weight loss (–2.1 kg vs +0.2 kg; $p<.01$) at post-treatment and at FUP (–1.9 kg vs +3.0 kg; $p<.001$). Depression/Associated Psychopathology A significant reduction in depression scores (HAM-D) occurred for both groups at week 8, but only the imipramine group showed maintenance of improvements at the 32-week follow-up. Imipramine was associated with greater reductions in depression at both timepoints ($p < .02$ at 8 weeks, $p<.001$ at 6-months FUP).
Agras et al (1994) [46]	N=108 100% female Mean age: 45.0 yrs Mean BMI: 38.6	Drug class: Tricyclics Design: Additive Randomized allocation to one of three treatments: behavioral weight loss (WL) only for 9 months; CBT for 3 months followed by BWL for 6 months (CBT/WL); combination (CBT for 3 months followed by BWL for 6 months) plus **desipramine** added during last 6 months (CBT/WL-D. BWL delivered in 90-minute 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 mo 3-mo FUP	Country: USA Single-site trial Recruitment via media DSM-IV research criteria for BED, including OBE twice weekly for 6months	Repeated measures ANOVA to determine time-by-treatment interaction. Primary outcome variables were binge days and weight. Only subjects with data at each time point were used (N=84).	Attrition A total of 24/108 (22%) dropped out of treatment; 10/37 (27%) from WL, 6/36 (17%) from CBT/WL, and 8/36 (22%) from CBT/WL-D. Binge Eating and Weight Loss At 12 weeks, CBT had significantly greater reduction in binge eating than the WL group while the WL group had significantly greater weight loss (2.0 kg) than CBT group (gain of 0.7 kg). At 36 weeks, no significant group differences were found in binge day frequency or binge abstinence (WL = 19%, CBT/WL = 37%, CBT/WL-D = 41%, ns). Weight losses also did not significantly differ at 36 weeks: 6.0 kg (CBT/WL-D), 1.6 (CBT/WL) and 3.7 kg (WL). Depression /Associated Psychopathology At 24 weeks, desipramine was associated with lower disinhibition scores (TFEQ) compared to WL and both CBT/WL and CBT/WL-D had significantly lower hunger (TFEQ) scores than WL at 24 weeks, but these differences were not significant at 36 wks. No group differences were observed for dietary restraint (TFEQ) or depression (BDI scores) at any timepoint.

Study	Sample	Intervention	Trial Length	Recruitment/Diagnostic assessment	Study efficacy	Findings
White & Grilo (2013) [44]	N=61 100% female Mean age: 45.2 (drug) 43.1 (placebo) Mean BMI: 36.2 (drug) 35.4 (placebo)	Drug class: Aminoketone Placebo-controlled, double-blind RCT of **buproprion** Fixed dose of 300 mg/day	8 wks	Country: USA Single-site Recruitment via media advertisements for overweight women seeking weight loss and binge eating treatment SCID-I/P for DSM-IV BED, EDE-interview to confirm	Rate of change in binge frequency and weight changes (continuous data) between groups were tested with mixed- effects regression models (time-by- treatment). ITT analyses for categorical outcome of remission (28 days abstinence).	Attrition A total of 13% from the drug condition and 10% from the placebo condition withdrew from the study (n.s.). Binge Eating Significant reductions in weekly binge eating frequency occurred for both groups from 3.3 (3.3) to 0.8 (1.2) for drug condition vs. 3.0 (2.6) to 1.0 (1.5) for placebo, but no significant group differences in improvement were found. A total of 27% in the placebo condition versus 42% in the placebo condition achieved remission from binge eating (ns). Weight Loss Buproprion was associated with significantly greater weight loss (1.8% BMI loss) versus placebo (0.6% BMI loss). ED Psychopathology Both groups demonstrated improvement on the EDE and FCI, but no significant group differences were found. Depression/Associated Psychopathology No significant group differences existed for improvement on the BDI.

Note. BED = Binge Eating Disorder; FUP = Follow-up period; RCT = Randomized, placebo-controlled trial; ITT = Intent-to-treat; OBE = Objective binge episode; BWL = Behavioral weight loss; CBT = Cognitive-behavior therapy; BDI = Beck Depression Inventory; TFEQ = Three Factor Eating Questionnaire; BES = Binge Eating Scale; BSQ = Body Shape Questionnaire; EDE = Eating Disorder Examination; CGI = Clinical Global Improvement scale; HAM-D = Hamilton Depression Inventory; SCL-90 = Symptom Checklist-90; YBOCS-BE = Yale-Brown Obsessive-Compulsive Scale-Binge Eating.

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Table 4

Randomized, Placebo-Controlled Trials of Antiepileptics for Binge Eating Disorder (BED)

Study	Sample	Intervention	Trial Length	Recruitment/Diagnostic assessment	Study efficacy	Findings
McElroy et al. (2003) [47]	N=61 87% female Mean age: 40.9 (drug) 40.7(placebo) Mean weight (kg): 120.4 (drug) 123.4 (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 weeks.	14 wks	Country: USA Single-site trial Recruitment via media DSM-IV-TR established by SCID for DSM-IV	Primary analysis of efficacy was repeated-measures random regression with treatment-by-time as the measure group differences in rate of change of binge episode frequency/wk (change per unit of time). Endpoint analyses using ITT (LOCF) and completer analyses were secondary.	Attrition A total of 16/61 (43%) dropped out of treatment, 47% (14 of 30) from the drug condition and 39% (12 of 31) from the placebo condition. Binge Eating At baseline, OBE was 5.3 (2.8) for the drug condition and 6.3 (2.8) for the placebo condition. At 14 weeks, OBE frequency dropped below 1 OBEs/week for topiramate and just below 4 OBEs/week for the placebo group (exact endpoint data n/a). Rate of reduction in OBE frequency was significant with an advantage for topiramate ($p < .001$). In the ITT group, 64% in the drug condition versus 30% in the placebo condition were abstinent from binge eating ($p < .05$). Weight Loss A mean weight loss of 5.9 kg was reported for drug condition versus 1.2 kg for the placebo condition ($p<.001$). Depression/Associated Psychopathology The rate of decrease in depression levels did not differ between treatment groups (HAM- D). Topiramate was associated with greater rate of change for CGI severity scale and obsessions and compulsions on the YBOCS- BE scale.
McElroy et al. (2007) [48]	N= 394 84% female Mean age: 44.0 (drug) 45.0 (placebo) Mean BMI: 38.0 (drug) 39.0 (placebo)	Placebo-controlled, double-blind, flexible-dose RCT of **topiramate** Start dosage = 25mg/day Increased to 400 mg over 8-week period, or as tolerated End dosage mean= 300 mg/day	16 wks	Country: USA Multi-site trial (19 sites) Recruitment via media and clinical referrals DSM-IV criteria est. by SCID I/P and EDE-interview; moderate –to- severe BED defined as 3 binge days/wk in the 2 wks prior to randomization	Primary outcome was number of binge eating days/week. Longitudinal analyses comparing difference between groups in rate of change of weekly binge frequency during treatment estimated by random regression methods model (treatment by time interaction). Modified ITT (patients meeting 1 or more exclusion criteria) and ITT analyses also performed. Secondary analyses were two-way ANCOVAs, with treatment and site as	Attrition A total of 114/394 (29%) dropped out of treatment, 28% (n= 55 of 195) from the drug condition and 30% (n= 59 of 199) from the placebo condition. Binge Eating Binge days per week decreased from 4.6 to 0.9 in the drug condition and 4.6 to 2.2 in the placebo condition ($p<.001$). Topiramate had a significantly greater rate of reduction in binge eating than placebo. In modified ITT population, 58% in the drug condition versus 29% in the placebo condition were abstinent from binge eating days and episodes ($p<.001$). Weight Loss A significant time by treatment interaction was also reported for BMI showing advantage to topiramate. Weight loss was –4.5 (5.1 kg) for drug group versus a weight gain of 0.2 (3.2) kg for the placebo group. Depression/Associated Psychopathology

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					factors and baseline value as covariates to evaluate endpoint.	A significant time by treatment interaction was reported for TFEQ scores. Topiramate was associated with greater reduction for CGI-Severity, and obsessive and compulsive scores on the Y-BOCS- BE. No group differences were observed for depression (MADRS) or anxiety (HAM-A).
Claudino et al (2007)[49]	N=73 96% female Mean age: 41.1 (drug) 35.4 (placebo) Mean BMI: 37.4 (drug) 37.4 (placebo)	Design: Additive Placebo-controlled, double-blind RCT comparing **topiramate** versus placebo in combination with cognitive behavioral therapy. 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 Start dose: 25 mg/day for 14 days, increased to 200 mg/ day. Patients with limited clinical response in weight or binge eating were prescribed additional increments of 25 mg weekly up to maximum dose of 300 mg/day	21 wks	Country: Brazil Multi-site trial Recruitment via media DSM-IV criteria > 17 BES cut-off score	Primary outcome variables were: rate of change in weight, binge frequency per week, BES, and BDI. ITT analyses (random regression models, treatmentXtime interaction). Endpoint analyses (LOCF) and completer were secondary outcomes.	Attrition A total of 17/73 (23%) dropped out of treatment; 7/37 (19%) from topiramate and 10/36 (28%) from placebo. Binge Eating CBT+topiramate and CBT+placebo did not differ significantly in rate of reduction for binge eating or BES. Mean binge days/wk decreased from 4.2 (3.4) to 0.0 (0.2) for topiramate and from 3.4 (1.3) to 0.3 (0.6) in placebo (ns). CBT +topiramate and CBT+placebo did not differ significantly in binge eating severity (BES) scores. Endpoint remission rates were higher for topiramate vs placebo (84% vs 61%; p=.03, ITT). Weight Loss CBT+topiramate had significantly greater rate of weight loss than CBT+placebo by final visit (−6.8 kg vs – 0.9 kg; p<.001). Depression/Associated Psychopathology Depressive symptoms (BDI scores) were significantly reduced in both groups between pre-and-post timepoints, but no between-group differences in rate of change were observed.
McElroy et al. (2006) [52]	N=60 88% female Mean age: 44.8 (drug) 43.0 (placebo) Mean BMI: 42.7 (drug) 40.6 (placebo)	Placebo-controlled, double-blind, flexible-dose RCT of **zonisamide** Start dosage = 100mg/day Increased to 600 mg, as tolerated End dosage mean= 436 mg/day	16 wks	Country: USA Single-site trial Recruitment via media DSM-IV-TR criteria for BED established by SCID-I/P for Axis I disorders	Longitudinal analyses comparing rate of change of weekly binge episode frequency during treatment between groups (mean OBE per week) estimated by random regression methods model (treatment-by-time interaction, measure of effect). Secondary endpoint analyses included ITT	Attrition A total of 30/60 (50%) dropped out of treatment, 60% (n = 18 of 30) from the drug condition and 40% (n= 12 of 30) from the placebo condition. Binge Eating OBEs at baseline were 4.7 (1.4) for the drug group and 4.4 (2.0) for the placebo group. At 16 weeks, OBE frequency dropped below 2 OBEs/ week for both groups. Rate of reduction in OBE frequency was significantly greater in the zonisamide group (p = .02). Endpoint analyses for binge frequency were not significant.

Study	Sample	Intervention	Trial Length	Recruitment/Diagnostic assessment	Study efficacy	Findings
					(LOCF) analyses. Exact trend test for response categories.	In the ITT groups, 54% in the drug condition versus 45% in the placebo condition were abstinent from binge eating (ns). Weight Loss A mean weight loss of 4.8 kg was reported for drug condition versus 1.0 kg for the placebo condition, which was a significantly greater rate of reduction and endpoint (p<.001). Depression/Associated Psychopathology Zonisamide was associated with a significantly greater rate of reduction for TFEQ disinhibition scores, CGI-severity ratings and obsessions (YBOCS-BE), but not depression (HAM-D) or TFEQ cognitive restraint.
Guerdjikova et al. (2009) [51]	N=51 Mean age: 46.1(drug) 42.9 (placebo) Mean BMI: 38.72 (drug) 41.52 (placebo)	Placebo-controlled, double-blind RCT of **lamotrigine.** Flexible-dose starting at 25 mg/day Mean endpoint of 236 mg/day	16 weeks	Country: USA Single-site Recruitment via media SCID for DSM-IV BED	Longitudinal analyses comparing rate of change of weekly binge frequency during treatment between groups (mean OBE per week) estimated by random regression methods model (treatment by time interaction). Secondary endpoint analyses included ITT (LOCF) analyses.	Attrition A total attrition rate of 44% (11/26) occurred for the drug condition and 29% (7/25) from the placebo condition (ns). Binge Eating Binges per week decreased from 3.92 (1.47) to 1.65 (2.35) in the drug condition vs. 3.28 (1.31) to 0.76 (1.71) for placebo (p=.ns). No difference in rate of change for binge eating or any other measure was detected between groups. 75% in the placebo condition versus 52% in the drug condition achieved remission from binge eating, indicating a strong placebo effect. Weight Loss Mean BMI changed non-significantly from 38.72 (5.38) to 38.24 (5.70) in the drug condition versus 41.52 (7.24) to 41.50 (7.42) in the placebo condition (p=ns). Depression/Associated Psychopathology No significant group differences were found in YBOCS, EDE-Q, BIS, MADRS, CGI, TFEQ.

Note. BED = Binge Eating Disorder; FUP = Follow-up period; RCT = Randomized, placebo-controlled trial; ITT = Intent-to-treat; OBE = Objective binge episode; BWL = Behavioral weight loss; CBT = Cognitive-behavior therapy; BDI = Beck Depression Inventory; TFEQ = Three Factor Eating Questionnaire; BES = Binge Eating Scale; BSQ = Body Shape Questionnaire; EDE = Eating Disorder Examination; CGI = Clinical Global Improvement scale; HAM-D = Hamilton Depression Inventory; SCL-90 = Symptom Checklist-90; YBOCS-BE = Yale-Brown Obsessive-Compulsive Scale-Binge Eating; RSE = Rosenberg Self-Esteem Scale.

Expert Opin Emerg Drugs. Author manuscript; available in PMC 2015 March 01.

Table 5

Randomized, Placebo-Controlled Trials of Anti-obesity and Other Agents for Binge Eating Disorder

Study	Sample	Intervention	Trial Length	Recruitment/Diagnostic Assessment	Study efficacy	Findings
Golay et al (2005) [53]	N=89 91% female Mean age: 41.2 (drug) 40.6 (placebo) Mean BMI: 35.7 (drug) 37.3 (placebo)	Drug class: Anti-obesity Design: Additive Placebo-controlled, double-blind RCT comparing **orlistat** versus placebo in combination with mildly hypo-caloric diet. Fixed dosage of 120 mg three times daily. Hypocaloric diet prescribed individually. 600kcal/day subtracted from estimated daily energy expenditure.	24 wks	Country: Switzerland Two-site trial Recruitment via clinics DSM-IV criteria for BED. Semi-structured interview by trained clinician.	Intent-to-treat analyses. ANCOVA to determine differences in weight loss between groups. Primary efficacy endpoint was percentage change in weight at week 24.	Attrition A total of 18/89 (20%) dropped out of treatment; 5/44 (11%) from orlistat and 13/45 (29%) from placebo. Binge Eating Orlistat+diet and placebo+diet did not differ significantly in binge frequency reduction (5.4 to 1.0 per week vs 6.2 to 1.7 per week, respectively). No significant group differences in the proportion still meeting BED diagnosis (29% for orlistat versus 23% for placebo). Weight Loss Orlistat+diet had significantly greater % weight loss than placebo+diet (−7.4% vs −2.3%; p<.001). Depression/Associated Psychopathology Orlistat+ diet showed a greater reduction in EDI-2 scores at week 24 compared to placebo + diet. No significant group differences were observed for depression or anxiety scores or quality of life (BDI, HAD, NHP).
Grilo, et al. (2005) [54]	N=50 88% female Mean age: 45.2 (drug) 47.0 (placebo) Mean BMI: 36.2 (drug) 36.8 (placebo)	Drug class: Anti-obesity Design: Additive Placebo-controlled, double-blind RCT comparing **orlistat** versus placebo in combination with cognitive behavioral therapy delivered using guided self-help (CBTgsh). Fixed dosage of 120 mg three times daily. CBTgsh delivered using patient self-care CBT book plus six (15-min) individual sessions.	12 weeks 3-mo FUP	Country: USA Single-site trial Recruitment via media DSM-IV research criteria for BED established by SCID-I/P for DSM-IV Axis I disorders and confirmed by EDE-interview.	Primary outcome were: remission (zero OBE during past 28/ days), and weight loss (categorical 5% loss). ITT analyses (BOCF) and completer analyses. For continuous data, ANCOVAs using baseline levels as covariates were used.	Attrition A total of 11/50 (22%) dropped out of treatment; 6/25 (24%) from orlistat and 5/25 (20%) from placebo (ns). Binge Eating Binge episodes decreased across timepoints (pre-tx, post-tx, 3-mo FUP) from 16.4 to 3.2 to 3.4 for the orlistat+CBTgsh versus 13.5 to 3.6 to 2.8 for the placebo+CBTgsh group. In ITT analyses, 64% in orlistat+CBTgsh versus 36% in placebo+CBTgsh achieved remission (p=.05) at posttreatment. But at 3-month FUP, 52% of both groups reached abstinence (ns). Weight Loss A total of 36% of orlistat + CBTgsh achieved a 5% weight loss at post-treatment versus 8% of placebo + CBTgsh (p=.02). At 3-month FUP, rates were 32% vs 8%, respectively (p=.03). Depression/Associated Psychopathology Significant improvement for both groups on the EDE-Q, RSE, and BDI occurred, but no significant group differences were detected in the magnitude of improvement.
Grilo & White (2013)[55]	N=40 Mono-lingual Hispanics 77.5% females Mean age:	Drug class: Anti-obesity Design: Additive Placebo- controlled, double-blind RCT	12 weeks 6-mo FUP	Country: USA Single-site trial Recruitment via community mental health center	Primary outcome variables were BMI loss, EDE, BDI, and binge eating frequency.	Attrition A total of 11/40 (27.5%) dropped out of treatment. Binge Eating A total of 60% in orlistat+BWL versus 70% in placebo+BWL achieved remission at

Study	Sample	Intervention	Trial Length	Recruitment/Diagnostic Assessment	Study efficacy	Findings
	45.9 (drug+BWL) 45.9 (drug+BWL) 45.6 (placebo +BWL) Mean BMI: 39.0 (drug+ BWL) 37.2 (placebo +BWL) Note: An additional N=39 obese patients without BED were also randomized to the treatments. Those N=39 non-BED patients are not considered in the present review. The reader is referred to the publication for findings which notably included BED status as a significant predictor and moderator of outcomes.	comparing **orlistat +** BWL versus placebo +BWL Fixed dosage of 120 mg three times daily. BWL treatment was a culturally- enhanced adaptation of the Diabetes Prevention Program		DSM-5 criteria est. by SCID-I/P and EDE interview following LEAD standard	ITT analyses using mixed models (treatment X time).	posttreatment. At 6-month FUP, 50% of both groups were in remission (ns). Weight Loss Mean BMI for both groups decreased significantly from 39.0 (7.0) to 37.9 (6.9) for orlistat + BWL and from 37.2 (5.3) to 36.0 (5.0) for placebo + BWL. Adding orlistat to BWL was not associated with greater improvement in weight loss than BWL + placebo. Depression/Associated Psychopathology Mean BDI scores for both groups decreased significantly from 22.9 (12.0) to 11.4 (12.0) for the orlistat + BWL and from 25.7 (10.6) to 17.7 (12.0) for placebo + BWL but no group differences were detected. Adding orlistat to BWL was not associated with greater improvement in depression or eating disorder psychopathology than BWL + placebo.
McElroy et al. (2013) [57]	N=62 Gender distribution not reported Mean age: 40.6 (drug) 48.6 (placebo) Mean BMI: 38.6 (drug) 39.2 (placebo)	Drug class: Anti-craving Placebo-controlled, double-blind RCT of **ALKS-33** Fixed-dose of 10 mg/ day, but 1 dose decrease to 5 mg/day permitted in event of poor tolerability	6 weeks	Country: USA Multi-site 2 academic ED programs and 4 private research centers SCID-P for DSM-IV-TR BED	Longitudinal analyses comparing rate of change of weekly binge frequency during treatment between groups (mean OBE per week) estimated by random regression methods model (treatment by time interaction). Secondary endpoint analyses included ITT (LOCF) analyses.	Attrition A total attrition rate of 50% (16/32) from the drug condition and 11% (4/37) from the placebo condition. Binge Eating Change in binges per week was –3.3 (2.4) for the drug condition and –3.2 (1.8) for the placebo condition (ns). A total of 35% (9 of 26) in the drug condition versus 53% (19 of 36) in the placebo condition achieved remission from binge eating (p= ns). Weight Loss Mean weight loss (kg) was –0.03 (2.02) for the drug condition and –0.23 (3.16) for the placebo condition (ns). Depression/Associated Psychopathology No significant group differences were found on any outcome measure (i.e., YBOCS, TFEQ, FCI, BDI, CGI).
McElroy et al	N=40 85% female Mean age:	Drug class: Anti-craving	10 weeks	Country: USA Single-site Recruitment via media	Longitudinal analyses comparing rate of change of	Attrition A total attrition rate of 25% (5/20) from the drug condition and 55% (11/ 20) from placebo.

Study	Sample	Intervention	Trial Length	Recruitment/Diagnostic Assessment	Study efficacy	Findings
(2011) [56]	46.2(drug) 45.8 (placebo) Mean BMI: 39.7 (drug) 39.2 (placebo)	Placebo-controlled, double-blind RCT of **acamprosate** Flexible dose starting at 1998 mg/day Increased to a maximum dosage of 2997 mg/day.		SCID for DSM-IV-TR BED	binge frequency during treatment between groups (mean OBE per week) estimated by random regression methods model (treatment by time interaction). Secondary endpoint analyses included completer and ITT (LOCF) analyses.	Binge Eating Same rate of reduction in OBE per week was found for both groups. Binges per week decreased from 4.5 (2.1) to 1.9 (2.4) in the drug condition vs. 4.5 (2.2) to 2.8 (2.5) for placebo (p= ns). A total of 32% in the drug condition versus 20% in the placebo condition achieved remission from binge eating (p=.ns). Weight Loss Mean BMI changed non-significantly from 39.7 (7.7) to 39.7 (7.4) in the drug condition versus 39.2 (8.4) to 39.7 (8.9) in the placebo condition (p = ns). ED Psychopathology No significant group differences existed for rate of change for any measure. Endpoint analyses showed no advantage for TFEQ, but acamprosate was associated with significant improvement on FCI, for which scores decreased from 82.2 (16.7) to 59.5 (15.6) in the drug condition from 79.4 (18.0) to 69.7 (22.7) for the placebo condition (p=.01). Depression/Associated Psychopathology No significant group differences existed for the rate of change for any measure. Endpoint analyses showed no advantage for CGI, but acamprosate was associated with significant improvement on YBOCS and SF-12 Mental Health scores.
McElroy et al. (2007) [58]	N=40 83% female Mean age: 43.1 (drug) 39.2 (placebo) Mean BMI: 37.3 (drug) 41.4 (placebo)	Drug class: ADHD Placebo-controlled, double-blind, flexible-dose RCT of **atomoxetine** Start dosage = 40 mg/day Increased to 80 mg in 2nd week Increased to 120 mg/day in 3rd week, or as tolerated End dosage mean= 106 mg/day	10 weeks	Country: USA Single-site trial Recruitment via media SCID for DSM-IV-TR	Longitudinal analyses comparing rate of change of binge frequency during treatment between groups (mean OBE per week) estimated by random regression methods model (treatment by time interaction). Endpoint analyses included completer and ITT (LOCF) analyses.	Attrition A total of 15/40 (38%) dropped out of treatment, 30% (n= 6 of 20) from the drug condition and 45% (n= 9 of 20) from the placebo condition. Binge Eating OBE frequency at baseline was 4.2 (1.4) for the drug group and 4.9 (2.5) for the placebo group. At 10 weeks, OBE frequency dropped below 2 OBEs/ week for both groups. Rate of reduction in OBE frequency was reported significantly greater for atomoxetine (p <.001). A total of 70% in the drug condition versus 32% in the placebo condition reached abstinence from binge eating (p<.05, ITT analysis). Weight Loss Weight loss was 2.7 (3.7) kg for drug condition and 0.0 (3.2) in placebo condition (p<.05, ITT). ED Psychopathology No significant difference in rate of improvement was found for TFEQ scores for cognitive restraint or disinhibition between groups but significant improvement associated with atomoxetine for TFEQ-hunger scales. Depression/Associated Psychopathology There was no difference in the rate of improvement in depression (HAM-D) scores between groups. Atomoxetine was associated with a significantly

Expert Opin Emerg Drugs. Author manuscript; available in PMC 2015 March 01.

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						greater rate of improvement for obsessions (YBOCS-BE) and CGI severit
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Brownley et al. (2013)[59]	N= 24 83% female Mean age: 36.6 (10.6) (total) Mean BMI: 34.2 (5.4) (total)	Drug class: Dietary supplement Placebo-controlled, double-blind RCT of **chromium picolinate (CrPic)** Patients allocated to high dose (1000 mg/day), moderate dose (600 mg/day) or placebo.	6 mo	Country: USA Single-site trial Recruitment via media SCID-I/P, confirmed with EDE	Mixed effects linear regression models to estimate mean change over 6-months: OBE/28 days, weight, depression, fasting glucose.	Attrition A total of 5/24 (21%) withdrew prior to the post-treatment visit. Binge Eating Binge frequency declined over time for all groups, with the largest magnitude in reduction for the high-dose group. The high dose group mean reduction was –1.65 (0.76) binges/month vs. –0.93 (0.70) for the moderate dose group and –0.97 (0.78) for placebo, but differences were not significant. Weight Loss 8/14 (57%) of the treatment groups lost weight whereas 7/7 (100%) of placebo gained weight. Estimated mean weight loss was –0.23 (–0.21) kg for the high dose and –0.13 (0.18) kg/month for the moderate dose group. Fasting glucose was significantly reduced in both the moderate and high-dose CrPic groups vs. placebo. Depression/Associated Psychopathology Rate of decline in EDE-Q scores was greater in the high dose group vs. placebo. No significant pairwise comparisons between groups were detected. Depression declined in all three groups, but differences were not significant.

Note. BED = binge eating disorder; FUP = follow-up period; RCT = randomized, placebo-controlled trial; ITT = intent-to-treat analysis; OBE = objective binge episode; BWL = behavioral weight loss; CBT = cognitive-behavior therapy; BDI = Beck Depression Inventory; TFEQ = Three Factor Eating Questionnaire; BES = Binge Eating Scale; BSQ = Body Shape Questionnaire; EDE = Eating Disorder Examination; CGI = Clinical Global Improvement scale; HAM-D = Hamilton Depression Inventory; SCL-90 = Symptom Checklist-90; YBOCS-BE = Yale-Brown Obsessive-Compulsive Scale-Binge Eating; RSE = Rosenberg Self-Esteem Scale.