Journal of Affective Disorders 338 (2023) 526–545

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review Article

Psychopharmacology of eating disorders: Systematic review and meta-analysis of randomized controlled trials

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ARTICLE INFO

Keywords:
Anorexia nervosa
Bulimia nervosa
Binge eating disorder
Psychopharmacology
Systematic review
meta-analysis

ABSTRACT

Background: The concurrent assessment of weight and affective psychopathology outcomes relevant to the psychopharmacology of major eating disorders (EDs), namely anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED), warrants systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods: PubMed, Scopus, and ClinicalTrials.gov were inquired from inception through August 31st, 2022, for RCTs documenting any psychopharmacological intervention for EDs diagnosed according to validated criteria and reporting weight and psychopathology changes. Adopted keywords were: "*anorexia nervosa*," "*bulimia nervosa*," "*binge eating disorder*," "*antidepressant*," "*antipsychotic*," *and* "*mood stabilizer*." No language restriction applied.

Results: 5122 records were identified, and 203 full-texts were reviewed. Sixty-two studies entered the qualitative synthesis (AN = 22, BN = 23, BED = 17), of which 22 entered the meta-analysis (AN = 9, BN = 10, BED = 3). Concerning BMI increase in AN, olanzapine outperformed placebo (Hedges'g = 0.283, 95%C·I. = 0.051–0.515, I^2 = 0 %; p = .017), whereas fluoxetine failed (Hedges'g = 0.351, 95%C.I. = −0.248 to 0.95, I^2 = 63.37 %; p = .251). Fluoxetine not significantly changed weight (Hedges'g = 0.147, 95%C.I. = −0.157–0.451, I^2 = 0 %; p = .343), reducing binging (Hedges'g = 0.203, 95%C.I. = 0.007–0.399, I^2 = 0 %; p = .042), and purging episodes (Hedges'g = 0.328, 95%C.I. = −0.061–0.717, I^2 = 58.97 %; p = .099) in BN. Lisdexamfetamine reduced weight (Hedges'g = 0.259, 95%C.I. = 0.071–0.446, I^2 = 0 %; p = .007) and binging (Hedges'g = 0.571, 95%C.I. = 0.282–0.860, I^2 = 53.84 %; p < .001) in BED.

Limitations: Small sample size, short duration, and lack of reliable operational definitions affect most of the included sponsored RCTs.

Conclusions: The efficacy of different drugs varies across different EDs, warranting additional primary studies recording broad psychopathological and cardiometabolic outcomes besides weight, especially against established psychotherapy interventions.

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https://doi.org/10.1016/j.jad.2023.06.068
Received 13 November 2022; Received in revised form 17 June 2023; Accepted 28 June 2023
Available online 30 June 2023

1. Introduction

The lifetime and 12-month prevalence rates of eating disorders (EDs) vary across geographic regions and sources (Qian et al., 2021). EDs are characterized by eating behaviors and psychological disorders leading to weight changes and/or social problems affecting the quality of life and social functioning (Treasure et al., 2020). Existing guidelines appraise nutritional counseling, psychotherapy, and medical complications beyond sole pharmacological management, establishing psychotherapy as the cornerstone treatment for different EDs (Treasure et al., 2020). Specifically, different psychotherapies have been developed to manage EDs: among other approaches and targets, family-based therapy seems to be particularly effective for young patients with anorexia nervosa (AN) (Lock et al., 2010), while bulimia nervosa (BN) and binge eating disorder (BED) would benefit from cognitive-behavioral therapy (CBT), in particular (Craighead, 1991). However, adulthood AN often poorly responds to psychotherapy (Arcelus et al., 2011), as do BN or BED (Hay et al., 2009; Wilson, 2011) (Yager, 1995). Up to one-third of the patients with remitted AN or BN would ultimately recur (Richard et al., 2005).

Therefore, integrative approaches are warranted for those EDs failing to respond satisfactorily to different psychological interventions. Many people with EDs receive pharmacotherapy in the real-world clinical setting (Edge and Gold, 2014; Reas, 2021). However, evidence-based pharmacotherapy for EDs is lacking compared to other psychiatric disorders (Hay, 2020; Hay et al., 2014).

Existing meta-analyses (MAs) assessing the randomized controlled trials (RCTs) for different pharmacological interventions (Cassioli et al., 2020) (Hilbert et al., 2020) (Svaldi et al., 2019) fail to concurrently appraise different EDs and specific psychopathological outcomes, as reflected by a recent umbrella review (UR) on the matter (Leichsenring et al., 2022), thus representing the aim of the present systematic review (SR) and MA.

2. Methods

The present SR and MA of RCTs followed the procedures outlined in the 2009 edition of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). The International Prospective Register of Systematic Reviews (PROSPERO) (https://www.crd.york.ac.uk/PROSPERO/) protocol is CRD42022 309075. Supplementary information is available on request from the authors.

2.1. Information sources and search strategy

Four authors divided into two independent teams (MF, AM & MB, MDP) searched PubMed, Scopus, and ClinicalTrials.gov (completed results posted) databases for records indexed from inception until January the 9th, 2022. The following string was searched in PubMed: (((((“eating disorder”[Title/Abstract]) OR (“eating disturbance”[Title/Abstract])) OR (“anorexia”[Title/Abstract])) OR (“bulimia”[Title/Abstract])) OR (“binge eating”[Title/Abstract])) AND ((((((((“pharmacological treatment”[Title/Abstract]) OR (“pharmacological therapy”[Title/Abstract])) OR (“pharmacotherapy”[Title/Abstract])) OR (“antidepressant”[Title/Abstract])) OR (“antipsychotic”[Title/Abstract])) OR (“anticonvulsant”[Title/Abstract])) OR (“mood stabilizer”[Title/Abstract])) OR (“lithium”[Title/Abstract])). Contact with authors was attempted whenever needed. Relevant cross-references, textbooks, and other materials were likewise appraised.

2.2. Inclusion criteria

We considered original peer-reviewed studies conducted in humans, both sexes, of any age, that included in-/out-patients with a diagnosis of AN, BN, or BED validated by a (semi-)structured interview validated according to either the Diagnostic and Statistical Manual of Mental Disorders (DSM) (any edition, or text revision) or the International Classification of Diseases (ICD) (any edition).

We included only RCTs, documenting any pharmacological intervention in participants with AN, BN, or BED, controlled with a placebo, active treatment, or treatment-as-usual (TAU). No language restrictions were applied.

2.3. Outcome measures

Primary efficacy outcomes were full or partial remission, as defined for AN, BN, and BED according to the DSM, any edition. Additional outcomes included the following scales for the specific EDs psychopathology over the trial: i) the Eating Disorder Examination (EDE) (Fairburn et al., 1993) or its auto-administered version, the EDE-Questionnaire (EDE-Q) (Fairburn and Beglin, 1994); ii) the Eating Disorder Inventory (EDI) (Garner DM, 1984), or the Eating Disorder Inventory-2 (EDI-2) (Yager et al., 2002); iii) the Bulimic Inventory Test (BITE) (Henderson and Freeman, 1987); iv) the Three-Factor Eating Questionnaire (TFEQ) (Stunkard, 1985); v) the Binge Eating Scale (BES) (Timmerman, 1999). Acceptability (discontinuation due to any cause) was likewise considered.

Secondary outcomes included: i) body weight records: Body Mass Index (BMI), weight, Expected Body Weight (EBW); ii) daily caloric intake; iii) frequency of binge episodes during the seven days preceding the interview, or the number of days without binge episodes, during one week-period; iv) frequency of compensatory behaviors (i.e. self-induced vomiting, fasting, misuse of laxatives or diuretics, excessive exercise) during the seven days preceding the interview, or the number of days without compensatory behaviors, during one week-period; v) depressive symptoms, measured through the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), the Beck Depression Inventory (BDI) (Beck et al., 1961), the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979), the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977), and the depression subscale of the Personality Assessment Inventory (PAI) (Morey, 2007); vi) obsessive-compulsive symptoms, measured through the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989) and the Yale-Brown Cornell Eating Disorder Scale (Y-BCEDS) (Mazure et al., 1994); vii) anxiety symptoms, measured through the Zung Anxiety Inventory (ZAI) (Zung, 1971), the Beck Anxiety Inventory (BAI) (Beck et al., 1988), and the anxiety subscale of the PAI (Morey, 2007).

2.4. Study selection and data extraction

Four authors divided into two teams (MF, AM & MB, MDP) independently extracted data using a purpose-built data extraction spreadsheet. Relevant full-texts were retrieved upon overall title/abstract screening. Contact with the authors was planned as necessary.

Data were sought for the following characteristics: Participants, Interventions, Comparisons, Outcomes, and Study design (PICOS).

Additional clinical variables were author(s), year of publication, geographical region of the study, sample size (total, cases, and controls), sex, adopted diagnostic coding and structured interview, setting (in-patients, outpatients), pharmacological class, mean dose of the drug, trial duration (in weeks), sponsorship information, study design (i.e., cross-over, or not), age at onset, ED severity at baseline, drop-out rate. Whenever possible, all the above clinical variables were compared between cases and controls, reporting mean and standard deviation for quantitative variables at baseline and study endpoint.

2.5. Quality assessment

We assessed the quality of the included interventional studies using the Risk of Bias 2 (RoB2) tool of the Cochrane Collaboration Library (Sterne et al., 2019). Any disagreement was solved by consensus.

2.6. Meta-analysis

We pooled individual studies using Comprehensive Meta-Analysis® software (version 2) (Borenstein et al., 2005). Due to anticipated heterogeneity, we conducted random-effects MA and computed the Hedges'g for metric measures documented by RCTs, using 95 % confidence intervals (CIs). According to Rosenthal (1993), the pre-post correlation coefficient was fixed at 0.7. Publication bias was assessed via visual inspection of funnel plots and with the Egger bias tests (Egger et al., 1997). Finally, we planned sub-group and meta-regression analyses to investigate further potential moderators in case of high heterogeneity ($I^2 \geq 50$ % = high) (Higgins et al., 2003).

3. Results

Five thousand one hundred twenty-two records were identified at the title and abstract level overall. The screening process returned 62 studies eligible for qualitative synthesis. Overall, 22 out of 62 studies fetched quantitative information for meta-analytic synthesis. Please refer to Fig. 1 (study flow) for details. Please refer to Supplementary Figs 1–3 for detailed quality appraisal, Supplementary Table 1 for excluded full-text records with the reason(s), and Fig. 2 for a summary of the pooled effect sizes across different EDs.

3.1. Pharmacological treatment of anorexia nervosa

Twenty-two studies (Andries et al., 2014; Attia et al., 1998; Attia et al., 2011; Attia et al., 2019; Bissada et al., 2008; Brambilla et al., 1995b, 1995c; Brambilla et al., 2007a, 2007b; Court et al., 2010; Fassino et al., 2002; Gross et al., 1981; Hagman et al., 2011; Halmi et al., 1982; Halmi et al., 1986; Kafantaris et al., 2011; Kaye et al., 2001; Mondraty et al., 2005; Powers et al., 2012; Vandereycken and Pierloot, 1982; Vandereycken, 1984; Walsh et al., 2006) encompassing 854 patients dealt with AN fetched 24 comparisons. The publication range of the studies was 1981–2019, thus ranging from DSM-III (APA, 1980) to DSM-5 (APA, 2013) coding. The primary outcome of the included studies was weight gain, either assessed as a difference in BMI, % change in *Ideal Body Weight* (%IBW), or % change in *Average Body Weight* (%ABW). Two one-year studies (Kaye et al., 2001; Walsh et al., 2006) also accounted for "remission," essentially considered as long-term maintenance of a normal-range weight. Three RCTs were cross-over design studies (Andries et al., 2014; Vandereycken and Pierloot, 1982; Vandereycken, 1984).

Different psychometric measures were adopted across the included studies, as detailed in Table 1.

3.1.1. Antipsychotic treatment

Olanzapine was evaluated by seven studies (Attia et al., 2011; Attia et al., 2019; Bissada et al., 2008; Brambilla et al., 2007a, 2007b;

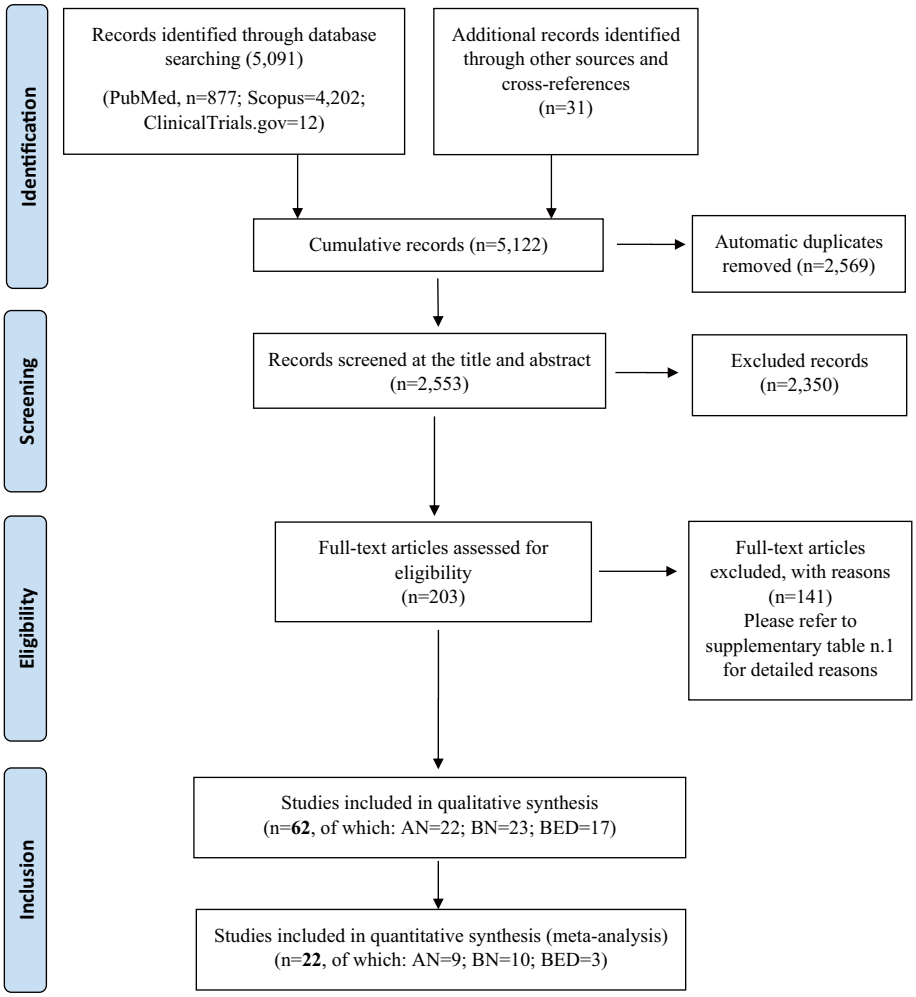

Fig. 1. Study flow diagram; PRISMA 2009, adapted.
From: Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6:e1000097.

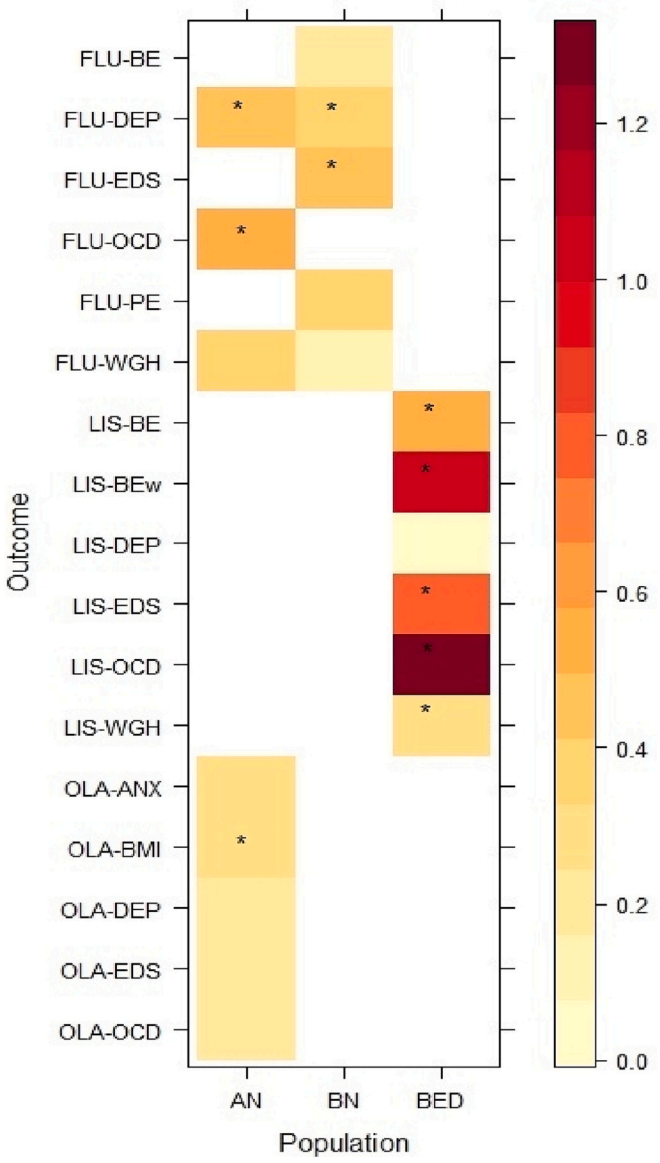

Fig. 2. Heatmap of pooled effect sizes vs. placebo. *denotes statistically significant Hedges'g values.
Legend for this figure: AN = Anorexia Nervosa; BN = Bulimia Nervosa: BED = Binge eating disorder; OLA = olanzapine; OCD = obsessive-compulsive disorder (-related symptomatology); EDS = eating disorder psychopathology; DEP = depressive symptoms; BMI = body mass index; ANX = anxious symptomtology; WGH = weight (change); LIS = lisdefamfetaimine; BEw = binge eating episodes, per week; BE = binging behavior; FLU = fluoxetine; PE = purging episodes.

Kafantaris et al., 2011; Mondraty et al., 2005), at an average dose = 7.26 mg/day (range, 5-10 mg/day). Overall, olanzapine led to a statistically significant weight gain (Attia et al., 2011; Attia et al., 2019; Brambilla et al., 2007a), or at least a faster one vs. placebo (Bissada et al., 2008), being well-tolerated (Attia et al., 2011; Kafantaris et al., 2011; Vandereycken and Pierloot, 1982; Vandereycken, 1984). However, no significant improvement over placebo was documented concerning the appraised psychopathology, except for one study (Brambilla et al., 2007a). On the other hand, the only olanzapine (10 mg/day) trial involving active control (chlorpromazine 50 mg/day) pointed towards a reduction of ruminative thoughts and anorexic conducts without significant weight gain over the 6–8 weeks trials (Mondraty et al., 2005).

Risperidone failed to lead to significant weight gain vs. placebo in adolescents with AN (Hagman et al., 2011). Similarly, quetiapine was ineffective for 21 women with AN across different outcomes (Powers et al., 2012). Yet, quetiapine effectively maintained the acute response regarding weight gain and psychopathological outcomes vs. TAU among people with AN; both cases and controls received psychotherapy and complained only of mild or transient side effects (Court et al., 2010). In addition, sulpiride (Vandereycken, 1984) and pimozide (Vandereycken and Pierloot, 1982) slightly outperformed the placebo for weight gain but failed to improve change-weight phobia and the distorted attitude towards the body. Please refer to Table 1 for details.

3.1.1.1. Meta-analysis of olanzapine treatment vs. placebo. Six studies (Attia et al., 2011; Attia et al., 2019; Bissada et al., 2008; Brambilla et al., 2007a, 2007b; Kafantaris et al., 2011) provided quantitative data about olanzapine vs. placebo, encompassing a total of 284 people, mean age = 25 years, of whom 98.6 % were females. The average duration of the trial was 12 weeks, while the mean dose of olanzapine was 6.71 mg/day (range: 5-10 mg/day). Two RCTs also delivered the sample weekly cognitive-behavioral therapy (CBT) treatment. The Hedges'g for BMI was 0.283 (95%C.I. = 0.051–0.515), $I^2 = 0$ %; $p = .017$, based on the six studies fetching six comparisons (Supplementary Fig. 4). No publication bias was detected, overall: *Egger test*: *beta* = 0.604, $p = .314$ (please see Supplementary Fig. 5).

Only three studies (Attia et al., 2011; Attia et al., 2019; Brambilla et al., 2007a) assessed the change in rating scales for ED psychopathology. Nonetheless, the mean reduction of relevant ratings failed to reach a statistically significant threshold: Hedges'g = 0.222 (95%C.I. = −0.049–0.494), $I^2 = 0$ %; $p = .109$, k = 3, comparisons = 3. Please see Supplementary Fig. 6. No publication bias was detected: *Egger test*: *beta* = 0.428, $p = .667$ (please see Supplementary Fig. 7).

Four studies fetching four comparisons (Attia et al., 2011; Attia et al., 2019; Bissada et al., 2008; Brambilla et al., 2007a) assessed obsessive-compulsive symptomatology, leading to Hedges'g = 0.171 (95%C.I. = −0.113–0.455), $I^2 = 11.02$ %; $p = .238$. Please see Supplementary Fig. 8 for details. No publication bias detected: *Egger test*: *beta* = 1.774, $p = .248$ (please see Supplementary Fig. 9).

Three studies fetching three comparisons (Attia et al., 2011; Attia et al., 2019; Bissada et al., 2008) assessed the depressive symptomatology using either the BDI, the CES-D, or the relevant subscale of the PAI. No statistically significant change was observed nonetheless: Hedges'g = 0.191 (95%C.I. = −0.078–0.46), $I^2 = 0$ %; $p = .165$. Please refer to Supplementary Fig. 10. No publication bias detected: *Egger test*: *beta* = 0.728, $p = .678$ (please see Supplementary Fig. 11).

The same RCTs assessed anxiety symptoms, showing the following non-statistically significant trend, based on three comparisons: Hedges'g = 0.263 (95%C.I. = −0.007–0.532), $I^2 = 0$ %; $p = .056$. Please refer to Supplementary Fig. 12. No publication bias detected: *Egger test*: *beta* = 0.433, $p = .839$ (please see Supplementary Fig. 13).

3.1.2. Antidepressant treatment

Fluoxetine was evaluated by three placebo-controlled studies (Attia et al., 1998; Kaye et al., 2001; Walsh et al., 2006). Two 52-week studies (Kaye et al., 2001; Walsh et al., 2006) assessed time-to-relapse, leading to non-concordant results: one (Kaye et al., 2001) showed that fluoxetine might help improve weight and psychopathological symptoms and in preventing relapse after weight restoration, while the other (Walsh et al., 2006) showed no significant difference between fluoxetine and placebo in time-to-relapse. A third 7-week study failed to demonstrate any benefit from fluoxetine vs. placebo in weight restoration and psychopathological improvement (Attia et al., 1998).

Head-to-head comparisons of fluoxetine vs. serotonin, norepinephrine multimodal agents (SNMAs) were documented in 2 studies: fluoxetine outperformed amineptine in 13 women with AN binge/purge-type (AN-BP) (Brambilla et al., 1995c), while it was less effective than nortriptyline in 22 women with AN restricting-type (AN-R) (Brambilla et al., 1995b).

Table 1
Qualitative analysis of psychopharmacological treatment in anorexia nervosa: 22 original records documented 24 comparisons overall.

Anorexia nervosa									
Authors, year	Population and type of AN, if specified; N = sample size	Mean age (years) Female %	Diagnosis DSM/ICD and type of interview	Duration of the trial and design	Active treatment (Mean dose)	Control group	Sponsorship	Main outcomes	Main findings
Andries et al., 2014 (Hagman et al., 2011)	Outpatients N = 24	Age: >18 F: 100 %	DSM-IV, clinical diagnosis	4 × 4 weeks; cross-over	Dronabinol (5 mg/day)	Placebo	No info	Weight, EDI-2	Dronabinol induced a small but significant weight gain without severe adverse events. No change in EDI-2 score.
Attia et al., 1998 (Halmi et al., 1982)	Inpatients N = 31	Age: 26 F: 100 %	DSM-IV, SCID	Seven weeks	Fluoxetine (56 mg/day) + psychotherapy	Placebo+psychotherapy	No info	%IBW, EAT, YBCEDS, ABS, BSQ, BDI, CGI, SCL-90	Compared to placebo, fluoxetine conferred no additional benefit to the treatment of underweight inpatients with AN.
Attia et al., 2011 (Halmi et al., 1982)	Outpatients *N* = 23	Age: 28 F: 96 %	DSM-IV, SCID	Eight weeks	Olanzapine (7.9 mg/day)	Placebo	Supported by the NIMH (R21MH069898). Eli Lilly & Co. supplied the medication as part of an investigator-initiated grant	BMI, EDI-2; EDE, YBCEDS, BSQ, BDI, BAI, PANSS, side effects	Olanzapine is generally well tolerated and may provide more benefit than placebo for outpatients with AN: greater increase of BMI in the olanzapine group but no improvement in psychological symptoms.
Attia et al., 2019 (Halmi et al., 1986)	Outpatients N = 152	Age: 29 F: 96 %	DSM-5, SCID	16 weeks	Olanzapine (7.8 mg/day)	Placebo	Supported, in part, by grant R01MH085921 from the NIMH. Eli Lilly & Co. provided pills but did not provide financial support	BMI, EDE, YBOCS, CESD, CGI, ZAI	A modest therapeutic effect of olanzapine versus placebo on weight but no significant benefit for psychological symptoms.
Bissada et al., 2008 (Halmi et al., 1986)	AN-R and AN-BP DH patients N = 34	Age: 27 F: 100 %	DSM-IV, clinical diagnosis	13 weeks	Olanzapine (6.6 mg/day)	Placebo	Supported by a grant from Eli Lilly	BMI, PAI, Y-BOCS	Not a significantly different improvement in the main outcomes between the two groups, but the olanzapine group achieved weight restoration faster.
Brambilla et al., 1995a (Kafantaris et al., 2011)	AN-BP outpatients N = 13	Age: 23 F: 100 %	DSM-III + IV, SCID	16 weeks; open-label	Amineptine (300 mg/day) + CBT + nutritional counseling	Fluoxetine (60 mg/day) + CBT + nutritional counseling	No info	BMI, EDI, BITE, HDRS, HARS	Both treatment groups improved psychopathology of ED, depression, anxiety, and weight, and better results were achieved with fluoxetine.
Brambilla et al., 1995b (Kaye et al., 2001)	AN-R outpatients N = 22	Age: 21 F: 100 %	DSM-III + IV, SCID	16 weeks; open-label	Nortriptyline (75 mg/day) + CBT + nutritional counseling	Fluoxetine (60 mg/day) + CBT + nutritional counseling	No info	BMI, EDI, BITE, HDRS, HARS	Psychopathology of ED, depression, anxiety, and weight improved in both treatment groups, and better results were achieved by nortriptyline.
Brambilla et al., 2007a (Mondraty et al., 2005)	AN-R and AN-BP outpatients N = 30	Age: 25 F: 100 %	DSM-IV, SCID	12 weeks	Olanzapine (5 mg/day) + CBT	Placebo+CBT	No info	BMI, EDI-2, YBCEDS, plasmatic homovanillic acid, HDRS	The pharmacological treatment can significantly improve specific aspects of AN: BMI, ED symptoms, depression, aggressiveness. No correlations were observed between homovanillic acid concentrations (increased in the olanzapine group) and psychopathological parameters.
Brambilla et al., 2007b (Powers et al., 2012)	Outpatients N = 20	Age: 23 F: 100 %	DSM-IV, SCID	12 weeks	Olanzapine (5 mg/day) + CBT + nutritional rehabilitation program	Placebo+CBT + nutritional rehabilitation program	The funding source is the Department of Psychiatry, Naples University, Second University, Naples, Italy	BMI, leptin, and ghrelin plasmatic levels	BMI increased significantly but not different in both treatment groups. No correlations were observed between BMI values and leptin and ghrelin levels, which did not change during treatment.

(*continued on next page*)

Table 1 (*continued*)

Anorexia nervosa									
Authors, year	Population and type of AN, if specified; N = sample size	Mean age (years) Female %	Diagnosis DSM/ICD and type of interview	Duration of the trial and design	Active treatment (Mean dose)	Control group	Sponsorship	Main outcomes	Main findings
Court et al., 2010 (Vandereycken and Pierloot, 1982)	Outpatients N = 33	Age: 22 F: 97 %	DSM-IV, clinical diagnosis	12 weeks; open-label	Quetiapine (323 mg/day) + TAU	TAU (CBT and IFST)	Astra Zeneca Pty Ltd. Australia provided funding through Investigator-Initiated Trial Funding	Side effects, EDI-2, BMI	Improvement in both groups (but only the quetiapine effects last at a follow-up of 6 months). Only mild and relatively minor side effects were reported (sedation, fatigue, poor concentration, orthostatic dizziness).
Fassino et al., 2002 (Vandereycken, 1984)	Outpatients N = 52	Age: 25 F: 100 %	DSM-IV, SCID	12 weeks; open-label	Citalopram (20 mg/day)	Waiting list	No info	EDI-2, SCL-90, BMI, weight, BDI, STAXI	Citalopram improves depression, obsessive-compulsive symptoms, impulsiveness, and anger in AN-R patients. In addition, weight gain was similar in the two groups.
Gross et al., 1981 (Walsh et al., 2006)	Outpatients N = 16	Age: 20 F: 100 %	DSM-III, clinical diagnosis	4–7 weeks	Lithium (corresponding to .9–1.4 mEq/L lithium serum level)	Placebo	No info	Weight, HSCL-90, denial, physical issues due to AN	Significant differences in weight gain between lithium and placebo groups at week 4 suggest a therapeutic effect and an improvement on general psychopathology assessments.
Hagman et al., 2011 (Agras, 1992)	Inpatients and DH patients; N = 40	Age: 16 F: 100 %	DSM-IV, clinical diagnosis	Nine weeks (mean)	Risperidone (2.5 mg/day)	Placebo	Supported by the Clinical Trials Research Center, Children's Hospital Colorado (M01RR00069), an investigator-initiated grant from Ortho-McNeil Janssen Scientific Affairs, LLC, for the study of medication, placebo and subject compensation and a grant from the Developmental Psychobiology Endowment Fund, University of Colorado School of Medicine (JH)	BMI, %IBW, EDI-2	No benefit for the addition of risperidone in adolescents with AN during the weight restoration phase of care.
Halmi et al., 1982 (Alger et al., 1991)	Inpatients N = 23	Age: 21 F: 100 %	DSM-III, clinical diagnosis	Four weeks	Amitriptyline (160 mg/day)	Placebo	No info	%IBW, HDRS	Amitriptyline resulted in no significant weight gain nor depression decrement compared to placebo, while cyproheptadine significantly affected weight and depressive symptoms.
Halmi et al., 1982 (Alger et al., 1991)	Inpatients N = 24	Age: 21 F: 100 %	DSM-III, clinical diagnosis	Four weeks	Cyproheptadine (32 mg/day)	Placebo		%IBW, HDRS	
Halmi et al., 1986 (Beumont et al., 1997)	Inpatients N = 48	Age: 21 F: 100 %	DSM-III, clinical diagnosis	Four weeks	Amitriptyline (160 mg/day)	Placebo	Supported by grants 5R01 MH26409 and 2R01 MH34105 from the NIMH, Bethesda, Md.	%IBW, ABS, HDRS, BDI, caloric intake	Amitriptyline group reported a significant effect on weight gain or depression when compared to placebo. Cyproheptadine significantly increased treatment efficiency for the non-bulimic patients and significantly impaired treatment efficiency for the bulimic patients compared with amitriptyline and placebo-treated groups.
Halmi et al., 1986 (Brambilla et al., 1995a)	Inpatients N = 49	Age: 21 F: 100 %	DSM-III, clinical diagnosis	Four weeks	Cyproheptadine (32 mg/day)	Placebo		%IBW, ABS, HDRS, BDI, caloric intake	
Kafantaris et al., 2011 (Carruba et al., 2001)	DH, in-, outpatients N = 20	Age: 17 F: 100 %	DSM-IV, clinical diagnosis	Ten weeks	Olanzapine (8.5 mg/day)	Placebo	Supported by an investigator-an initiated grant from Eli Lilly.	BMI, EDE, YBCEDS, side effects	The addition of olanzapine did not increase body weight and did not improve general psychopathology assessment in adolescents with AN-R. Group-by-time interactions were not significant. No safety concerns.

(*continued on next page*)

Table 1 (*continued*)

Anorexia nervosa									
Authors, year	Population and type of AN, if specified; N = sample size	Mean age (years) Female %	Diagnosis DSM/ICD and type of interview	Duration of the trial and design	Active treatment (Mean dose)	Control group	Sponsorship	Main outcomes	Main findings
Kaye et al., 2001 (Fahy et al., 1993)	AN-R In- and outpatients N = 35	Age: 22 F: 100 %	DSM-IV, clinical diagnosis	52 weeks	Fluoxetine (40 mg/day)	Placebo	Supported by a grant from Eli Lilly Corporation and the NIMH (Grants Nos. MH46001-03, MH42984-04, and MH46687)	Completers, relapse, %ABW, YBCEDS, HDRS, HARS	Those subjects with AN-R remaining on fluoxetine for a year significantly increased weight and reduced symptoms. Still, many participants dropped out of this study: 63 % of subjects remained on fluoxetine for a year, whereas only 16 % remained on the placebo.
Mondraty et al., 2005 (Faris et al., 2000)	Outpatients N = 15	Age: 25 F: 100 %	DSM-IV, clinical diagnosis	6–8 weeks; open-label	Olanzapine (10 mg/day)	Chlorpromazine (50 mg/day)	No info	Rumination (PI subscale), BMI, EDI-2	Olanzapine caused a more significant reduction in ruminative thinking than chlorpromazine, as well as in ED symptoms. There was no significant difference in weight gain between the two arms.
Powers et al., 2012 (Fichter et al., 1991)	Outpatients N = 21	Age: 34 F:100 %	DSM-IV, SCID	Eight weeks	Quetiapine (177.7 mg/day)	Placebo	No info	BMI, EDI-2, YBCEDS, HDRS, STAI, PANSS, YBOCS	No difference in outcome for any of the measures between groups. Quetiapine appeared to have little direct effect (no significant) on improving core eating disorder symptoms and secondary measures compared to placebo.
Vandereycken and Pierloot, 1982 (Fichter et al., 1997)	Inpatients N = 18	Age: 22 F: 100 %	DSM-III, clinical diagnosis	2 × 3 weeks; cross-over	Pimozide (5 mg/day) + BT	Placebo+BT	No info	Weight, ABS	Pimozide enhanced the weight gain promoted by behavioral therapy, but it negatively influenced the patients' attitudes judged on the rating scale used.
Vandereycken, 1984 (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992)	Inpatients N = 18	Age: 23.4 F: 100 %	DSM-III, clinical diagnosis	2 × 3 weeks; cross-over	Sulpiride (350 mg/day)	Placebo	No info	Weight, EAT, ABS	Regarding daily weight gain, sulpiride was superior to placebo. In the cross-over analysis, however, this effect did not reach statistical significance. It is far more essential to change weight phobia and distorted attitudes towards the body.
Walsh et al., 2006 (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992)	In- and outpatient N = 93	Age: 24 F: 100 %	DSM-IV, clinical diagnosis	52 weeks	Fluoxetine (70 mg/day) + CBT	Placebo+CBT	Supported in part by grants MH060271 and MH60336 from NIH.	Completers, time-to-relapse, BMI, EDI, YBCEDS, BAI, BDI	This study failed to demonstrate any benefit from fluoxetine in patients with the following weight restoration. There was no significant difference between fluoxetine and placebo in time-to-relapse, and weight decreased in both groups. Two suicide attempts were reported (1 patient with fluoxetine and one patient with placebo).

Legend: DSM: Diagnostic and Statistical Manual for mental disorders; DH: Day Hospital; SCID: Structured Clinical Interview for DSM; BMI: Body Mass Index; AN-BP: Anorexia Nervosa-Binge Eating-Purging type; AN-R: Anorexia Nervosa-Restricting type; TAU: Treatment As Usual; CBT: Cognitive-Behavioral Therapy; BT: Behavioral Therapy; EDE (Q): Eating Disorder Examination (Questionnaire); Y-BOCS: Yale Brown Obsessive Compulsive Scale; CESD: Centre for Epidemiologic Studies Depression Scale; CGI: Clinical Global Inventory; ZAI: Zung Anxiety Inventory; EDI (-2): Eating Disorder Inventory (2); Y-BCEDS: Yale Brown Cornell Eating Disorder Scale; HDRS: Hamilton Depression Rating Scale; STAI: State-Trait Anxiety Inventory; PANSS: Positive and Negative Symptoms Scale; BSQ: Body Shape Questionnaire; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; %IBW: % of Ideal Body Weight; PAI: Personality Assessment Inventory; STAXI: State-Trait Anger Expression Inventory; BITE: Bulimic Investigatory Test, Edinburgh; HARS: Hamilton Anxiety Rating Scale; ABS: Anorexia-Bulimia Spectrum; (H) SCL-90: (Hopkins) Symptom Checklist-90. NIMH: National Institute of Mental Health. NIH: National Institute of Health.

Amitriptyline was ineffective in 2 placebo-controlled studies (Halmi et al., 1982; Halmi et al., 1986). Citalopram outperformed the placebo in improving psychopathological symptoms in 25 women with AN without significantly affecting weight restoration over 12 weeks (Fassino et al., 2002).

3.1.2.1. Meta-analysis of fluoxetine treatment vs. placebo. Three studies (Attia et al., 1998; Kaye et al., 2001; Walsh et al., 2006) provided quantitative data about fluoxetine vs. placebo, encompassing 159 women, mean age = 22 years. One RCT included women with AN-R (Kaye et al., 2001). Two 52-week RCTs (Kaye et al., 2001; Walsh et al., 2006) included inpatients who continued the study after hospital discharge. A third 7-week study included only inpatients (Attia et al., 1998). The mean dose of fluoxetine was 55.33 mg/day (range: 40-80 mg/day). Two RCTs also delivered CBT and supportive psychotherapy to the included sample (Attia et al., 1998; Walsh et al., 2006). The Hedges'g for weight gain, in terms of BMI, or %IBW, or %ABW, was 0.351 (95%C.I. = −0.248–0.950), $I^2 = 63.37$ %; $p = .251$, based on the three studies fetching three comparisons (Supplementary Fig. 14). No publication bias was detected: *Egger test*: *beta* = 9.105 ($p = .249$) (please see Supplementary Fig. 15).

The same three RCTs assessed the depressive and obsessive-compulsive symptoms based on three comparisons. The depressive and the obsessive-compulsive symptomatology significantly improved with fluoxetine vs. placebo: Hedges'g = 0.549 (95%C.I. = 0.051–1.047), $I^2 = 53.38$ %; $p = .031$ (Supplementary Fig. 16), and Hedges'g = 0.416 (95%C.I. = 0.106–0.727), $I^2 = 0$; $p = .009$ (Supplementary Fig. 17), respectively. No publication bias was detected: for depressive symptomatology: *Egger test*: *beta* = 1.665 ($p = .758$) (please see Supplementary Fig. 18); for obsessive-compulsive symptomatology: *Egger test*: *beta* = −0.347 ($p = .9$) (please see Supplementary Fig. 19).

3.1.2.2. Sub-group analysis of fluoxetine treatment vs. placebo. Those patients exposed to fluoxetine alone vs. placebo significantly increased their body weight: Hedges'g = 0.831 (95%C.I. = 0.153–1.509), $I^2 = 0$ %; $p = .016$, k = 1 (Kaye et al., 2001). Those patients exposed to fluoxetine plus CBT vs. placebo plus CBT had smaller weight gain: Hedges'g = 0.117 (95%C.I. = −0.487–0.721), $I^2 = 49.374$ %; $p = .704$, k = 2 (Attia et al., 1998; Walsh et al., 2006). Please refer to Supplementary Fig. 20.

Those patients with AN-R significantly increased their body weight compared to those with AN not specified: Hedges'g = 0.831 (95%C.I. = −0.079–1.741), $I^2 = 0$ %; $p = .073$, k = 1 (Kaye et al., 2001) vs. Hedges'g = 0.117 (95%C.I. = −0.487–0.721), $I^2 = 49.37$ %; p = .704, k = 2 (Attia et al., 1998; Walsh et al., 2006). Please refer to Supplementary Fig. 21.

Sub-group analysis failed to show any significant impact of the concurrent CBT on depressive symptomatology, nor any statistically significant difference in the change of depression rating scales between different AN sub-types.

3.1.2.3. Meta-regression of fluoxetine treatment vs. placebo. Neither the mean duration of the trial nor the average age of the sample significantly affected weight gain. Meta-regression showed a statistically significant reduction in weight gain with a higher mean dose of fluoxetine (beta = −0.033, 95%C.I = −0.062 to −0.005, $p = .021$, $R^2 = 0$, k = 3). Please refer to Supplementary Fig. 22.

3.1.3. Dronabinol, cyproheptadine, and lithium treatment

Dronabinol was evaluated in one RCT (Andries et al., 2014): those patients receiving dronabinol experienced a significantly higher weight gain than those receiving placebo; however, the psychopathology underlying the disorder did not improve with dronabinol treatment.

Cyproheptadine was evaluated in 2 RCTs (Halmi et al., 1982; Halmi et al., 1986), showing higher efficacy vs. placebo in improving weight and psychopathological symptoms, especially depressive ones. However, upon stratification of the results for AN sub-types, AN-BP patients were the only worsening ones.

Finally, lithium was evaluated in one RCT (Gross et al., 1981), showing higher efficacy than a placebo in weight gain and general psychopathology in patients with AN.

Please refer to Table 1 for details.

3.2. Pharmacological treatment of bulimia nervosa

Twenty-three trials (Agras, 1992; Alger et al., 1991; Beumont et al., 1997; Brambilla et al., 1995a; Carruba et al., 2001; Fahy et al., 1993; Faris et al., 2000; Fichter et al., 1991, 1997; Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992; Goldbloom et al., 1997; Goldstein et al., 1995; Kanerva, 1995; Kennedy et al., 1993; Mitchell, 1984; Mitchell et al., 2001; Nickel et al., 2005; Pope Jr. et al., 1983; Pope Jr. et al., 1989; Romano et al., 2002; Walsh et al., 1991; Walsh et al., 2000; Walsh et al., 2004) encompassing 2006 patients dealt with BN fetching 26 comparisons. The publication range of the studies was 1983–2004, thus ranging from DSM-III to DSM-IV (APA, 1994). The primary outcomes of the included studies were the frequency of binge episodes (BEs) per week, the frequency of purging episodes (PEs) per week, and the number of days with at least one binge or purging episode within one week (days of binging/purging per week). Most RCTs considered the change in the score of different psychometric measures, as detailed in Table 2. ED-specific psychopathology was assessed using the EDE, the EDI, or the BITE. Depressive symptomatology was rated using the HDRS, the BDI, or the MADRS. Only 2 RCTs (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992; Goldstein et al., 1995), with a mean duration ranging from 8 to 16 weeks, also accounted for "remission," defined as the lack of dysfunctional eating behaviors.

One study (Brambilla et al., 1995a) compared amineptine vs. fluvoxamine, while 2 RCTs involved CBT augmentation of pharmacotherapy vs. CBT alone (Agras, 1992; Goldbloom et al., 1997).

3.2.1. Antidepressant treatment

Ten RCTs evaluated fluoxetine (Beumont et al., 1997; Fichter et al., 1991; Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992; Goldbloom et al., 1997; Goldstein et al., 1995; Kanerva, 1995; Mitchell et al., 2001; Romano et al., 2002; Walsh et al., 2000; Walsh et al., 2004). The mean dose was 60 mg/day, except for one arm of one RCT (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992), employing a mean dose = 20 mg/day. Fluoxetine proved safe and effective in reducing both the frequency of BEs and PEs, improving the psychopathological outcomes in three studies (Fichter et al., 1991; Goldstein et al., 1995; Romano et al., 2002). The efficacy of fluoxetine was higher for 60 mg than 20 mg daily exposures (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992).

Fluoxetine failed to outperform the placebo in one RCT only (Fichter et al., 1991), in which the included inpatients received intensive psychotherapy within the 5-week trial. A 16-week RCT (Goldbloom et al., 1997) comparing fluoxetine 60 mg/day vs. weekly CBT vs. fluoxetine 60 mg/day plus weekly CBT, demonstrated that CBT alone was slightly more effective than CBT plus fluoxetine, although failing a statistically significant threshold; CBT plus fluoxetine was significantly more effective than fluoxetine monotherapy. However, fluoxetine proved effective in those patients not responding to psychotherapy alone in a subsequent RCT (Walsh et al., 2000).

Concerning fluvoxamine, a mean daily dose = 188 mg effectively prevented relapse, but neither on depressive or anxious symptoms nor body perception (Fichter et al., 1997). Fluvoxamine 300 mg/day was as effective as amineptine 300 mg/day in reducing the BITE total score; amineptine outperformed fluvoxamine in removing anxious symptomatology (Brambilla et al., 1995a).

Among those studies involving SNMAs vs. placebo (Agras, 1992; Alger et al., 1991; Mitchell, 1984; Pope Jr. et al., 1983; Walsh et al., 1991), only imipramine 200 mg/day vs. placebo (Pope Jr. et al., 1983)

Table 2
Qualitative analysis of psychopharmacological treatment in bulimia nervosa: 23 original records documented 26 comparisons.

Bulimia nervosa									
Authors, year	Population N = sample size	Mean age (years) Female %	Diagnosis DSM/ICD and type of interview	Duration of the trial and design	Active treatment (Mean dose)	Control group	Sponsorship	Main outcomes	Main findings
Agras, 1992 (Goldbloom et al., 1997)	Outpatients N = 35	Age: 29 F: 100 %	DSM-III clinical diagnosis	24 weeks; single-blind	Desipramine (168 mg/day)	CBT only	Supported in part by NIMH grant MH-38637	BE/week; PE/week; BDI, EDI, EAT	The 24-weeks combined condition was superior to 16 weeks of medication. The combined condition appeared to reduce associated psychopathology, such as dietary preoccupation and lowering binge and purging frequency.
Alger et al., 1991 (Goldstein et al., 1995)	Outpatients *N* = 14	Age: 29 F: 100 %	DSM-III clinical diagnosis	Eight weeks	Imipramine (150-200 mg/day)	Placebo	Supported by a grant from the van Bethuysen Fund, Albany Medical College	BE/week; BE duration, weight, BDI	No significant change in duration and frequency of BE. Considerable reduction in BDI score.
Alger et al., 1991 (Kanerva, 1995)	Outpatients N = 15	Age: 28 F: 100 %	DSM-III clinical diagnosis	Eight weeks	Naltrexone (100-150 mg/die)	Placebo		BE/week; BE duration, weight, BDI	Compared to placebo, there was a significant reduction in binge duration but not binge frequency—considerable reduction in BDI score.
Beumont et al., 1997 (Kennedy et al., 1993)	Outpatients *N* = 67	Age: 23 F: 100 %	DSM-III clinical diagnosis	Eight weeks	Fluoxetine (60 mg/day) + nutritional counseling	Placebo+nutritional counseling	Funding by Eli Lilly Australia	BE/week, EDE, HDRS, EAT, EDI	Nutritional counseling is an effective means of treating BN, with improvement maintained up to 3 months of follow-up. The addition of fluoxetine may confer some benefits during active treatment, but its discontinuation may contribute to a higher recurrence rate.
Brambilla et al., 1995a, 1995b, 1995c (Mitchell, 1984)	Outpatients N = 15	Age: 22 F: 100 %	DSM-III SCID	16 weeks; open-label	Amineptine (300 mg/day) + CBT	Fluvoxamine (300 mg/day) + CBT	No info	EDI, BITE, HDRS, HARS	BITE symptoms and gravity scores improved significantly during both treatments, while EDI scores and depressive symptoms did not change significantly. Anxiety improved with amineptine, not with fluvoxamine therapy.
Carruba et al., 2001 (Mitchell et al., 2001)	Outpatients *N* = 77	Age: 25 F: 100 %	DSM-III clinical diagnosis	Six weeks	Moclobemide (600 mg/day)	Placebo	Supported in part by a grant from Roche	BE/week; PE/week; HDRS, TFEQ, side effects	Moclobemide can be safely administered but is not efficacious in reducing binging and purging episodes in bulimia nervosa patients.
Fahy et al., 1993 (Mitchell et al., 2001)	Outpatients *N* = 43	Age: 26 F: 100 %	DSM-III clinical diagnosis	Eight weeks	D-Fenfluramine (45 mg/day) + CBT	Placebo+CBT	Financial support by Les Laboratoires Servier	BE/week; PE/week; EAT, BITE MADRS	The study failed to show that adding fenfluramine affords an advantage over brief psychotherapy alone. D-fenfluramine is effective in suppressing overeating and excessive carbohydrate consumption. In BN it is not an effective treatment.
Faris et al., 2000 (Nickel et al., 2005)	Outpatients *N* = 26	Age: 29 F: 100 %	DSM-IV SCID	Five weeks	Ondansetron (24 mg/day)	Placebo	Supported by a grant from the Mark A Nugent Research Foundation (St Paul, MN, USA) and by R01DK42291	BE/week; PE/week; time spent on binging/purging, weight	A decrease in binge-eating and vomiting in the ondansetron group was not accompanied by compensatory changes in duration or number of binges. The symptom's improvement may Result from a pharmacological correction of abnormal vagal neurotransmission.
Fichter et al., 1991 (Pope Jr. et al., 1989)	Inpatients N = 40	Age: 25 F: 100 %	DSM-III SIABN	Five weeks	Fluoxetine (60 mg/day) + intensive behavioral psychotherapy	Placebo+intensive behavioral psychotherapy	No info	BE/week, EDI, SCL-90, CGI, HDRS, safety	Fluoxetine reduced body weight, especially during the first three weeks. No significant improvement in eating behavior and general psychopathology. It was generally well tolerated.

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Table 2 (*continued*)

Bulimia nervosa

Authors, year	Population N = sample size	Mean age (years) Female %	Diagnosis DSM/ICD and type of interview	Duration of the trial and design	Active treatment (Mean dose)	Control group	Sponsorship	Main outcomes	Main findings
Fichter et al., 1997 (Pope Jr. et al., 1983)	DH, in-, outpatients *N* = 72	Age: 24 F: 100 %	DSM-III clinical diagnosis	15 weeks	Fluvoxamine (188 mg/day)	Placebo	No info	CGI, HSCL, HDRS, EDI, relapse	Fluvoxamine had significant effects on preventing relapse as measured with CGI or HSCL but no significant effect on variables measuring depression, anxiety, or body perception.
Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992 (Romano et al., 2002)	Outpatients *N* = 258	Age: 27 F: 100 %	DSM-III Clinical diagnosis	Eight weeks	Fluoxetine (60 mg/day)	Placebo	Supported by a grant from Eli Lilly & Co, Indianapolis, Ind.	Remission; BE/week; PE/week; EDI HDRS, EAT	Fluoxetine 60 mg was superior to placebo in decreasing the frequency of BE and PE, depression, carbohydrates craving, and pathologic eating attitudes and behaviors. Fluoxetine 20 mg was superior to placebo but still less efficient than Fluoxetine 60 mg.
Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992 (Walsh et al., 1991)	Outpatients N = 258	Age: 27 F: 100 %	DSM-III Clinical diagnosis	Eight weeks	Fluoxetine (20 mg/day)	Placebo		Remission; BE/week; PE/week; EDI HDRS, EAT	
Goldbloom et al., 1997 (Walsh et al., 2000)	Outpatients *N* = 52	Age: 26 F: 100 %	DSM-III SCID	16 weeks; open-label	Fluoxetine (60 mg/day) + iCBT	iCBT only	She was supported by an operating grant from Eli Lilly Canada Inc.	BE/week, PE/week, EDE (shape concern + weight concern); BDI	The combination of pharmacotherapy and psychotherapy was superior to pharmacotherapy alone on specific parameters, and there was no significant advantage to the combination over psychotherapy alone.
Goldbloom et al., 1995 (Walsh et al., 2004)	Outpatients *N* = 398	Age: 27 F: 96 %	DSM-III clinical diagnosis	16 weeks	Fluoxetine (60 mg/day)	Placebo	No info	% of the change in BE and PE, Remission rate, CGI, HDRS, EDI, side effects	Compared with placebo, fluoxetine treatment resulted in a significantly greater reduction in vomiting and binge-eating episodes per week at the endpoint. Adverse events, vital signs, and laboratory analyses indicated that fluoxetine was safe.
Kanerva, 1995 (Appolinario et al., 2003)	Outpatients N = 50	Age: 25 F: 100 %	DSM-III Semi-structured interview	Eight weeks	Fluoxetine (60 mg/day)	Placebo	Supported by a grant from Eli Lilly & Co and the Helsinki University Central Hospital	Weight, EDI, BITE, EAT, HDRS, STAI	Fluoxetine was superior to placebo in decreasing HDRS score, eating-related symptoms, and reducing body weight.
Kennedy et al., 1993 (Brambilla et al., 2009)	Outpatients *N* = 36	Age: 27 F: 100 %	DSM-III SCID	Eight weeks;	Brofaromine (25-200 mg/day)	Placebo	No info	BE/week; PE/week; EDI, HDRS, HARS, side effects	Brofaromine produced a significant effect in decreasing episodes of vomiting (binge eating comparable in both groups). A significant proportion of the subjects on brofaromine lost weight compared with the placebo group. A high percentage of adverse events were reported in the brofaromine group.
Mitchell, 1984 (Brambilla et al., 2009)	Outpatients *N* = 32	Age: 25 F: 100 %	DSM-III clinical diagnosis	Eight weeks	Amitriptyline (150 mg/day)	Placebo	No info	BE/week; PE/week; HDRS	Improvement of BE in both groups. The active treatment group improved depressive symptoms more than the placebo group.
Mitchell et al., 2001 (Grant et al., 2019)	Outpatients N = 48	Age: 27 F: 100 %	DSM-III clinical diagnosis	16 weeks; single-blind	Fluoxetine (60 mg/day)	Placebo	Supported, in part, by a grant from Dista Pharmaceutical, NIMH Grant MH R01 43296, and a center grant on eating disorders	BE/week; PE/week; CGI; HDRS, EDI	Fluoxetine was superior to placebo in suppressing the target symptoms in subjects with BN.
Mitchell et al., 2001 (Grilo et al., 2005)	Outpatients N = 43	Age: 27 F: 100 %	DSM-III clinical diagnosis	16 weeks; single-blind	Fluoxetine (60 mg/day) +	Placebo+self-help manual		BE/week; PE/week;	Fluoxetine and the self-help manual effectively reduced the frequency of vomiting

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Table 2 (*continued*)

Bulimia nervosa									
Authors, year	Population N = sample size	Mean age (years) Female %	Diagnosis DSM/ICD and type of interview	Duration of the trial and design	Active treatment (Mean dose)	Control group	Sponsorship	Main outcomes	Main findings
					self-help manual		Research from the McKnight Foundation.	CGI; HDRS, EDI	episodes and improved response rates.
Nickel et al., 2005 (Grilo et al., 2005)	Outpatients *N* = 60	Age: 21 F: 100 %	DSM-IV SCID	Ten weeks	Topiramate (25-200 mg/day)	Placebo	No info	Binge/Purge episodes per week; weight; HRQOL; side effects	Topiramate appears to be safe (well-tolerated) and effective in influencing the frequency of binging/purging, body weight, and HROQL scores in bulimic patients.
Pope Jr. et al., 1989 (Grilo et al., 2021)	Outpatients *N* = 46	Age: 26 F: 100 %	DSM-III SCID	Six weeks	Trazodone (200-400 mg/day)	Placebo	Supported, in part, by a grant from Bristol-Myers Pharmaceuticals and by NIMH Clinical Research grant MH-36224	Percentage of the change in BE and PE, side effects	The drug proved significantly superior to the placebo in subjective improvement assessment measures of frequency of binge eating and vomiting.
Pope Jr. et al., 1983 (Guerdjikova et al., 2009)	Outpatients *N* = 22	Age: 28 F: 100 %	DSM-III clinical diagnosis	Six weeks	Imipramine (200 mg/day)	Placebo	No info	% of the change in binge frequency; HDRS	Imipramine was superior to placebo in reducing binge frequency in patients with bulimia nervosa.
Romano et al., 2002 (Guerdjikova et al., 2012)	Outpatients *N* = 150	Age: 30 F: 100 %	DSM-IV clinical diagnosis	52 weeks	Fluoxetine (20 mg/day)	Placebo	She was supported by a clinical research grant from Eli Lilly & Co.	BE/week; PE/week, time-to-relapse, CGI; HDRS, EDI, YBCEDS; safety	Continued treatment with fluoxetine in patients with bulimia nervosa who responded to acute treatment with fluoxetine improved outcomes and decreased the likelihood of relapse. No safety concerns.
Walsh et al., 1991 (Guerdjikova et al., 2016)	Outpatients *N* = 78	Age: 25 F: 100 %	DSM-III SCID	Six weeks	Desipramine (max 300 mg/day)	Placebo	Supported, in part, by NIMH grant MH-38355	BE/week, BMI, BDI, EAT, HDRS, SCL-90, STAI	Desipramine was superior to placebo in the short-term treatment of bulimia nervosa, with or without comorbid depression.
Walsh et al., 2000 (Hudson et al., 1998)	Outpatients N = 22	Age: 30 F: 100 %	DSM-III clinical diagnosis	Eight weeks	Fluoxetine (60 mg/day)	Placebo	She was supported in part by NIMH grant MH-49,877 to Drs. Walsh and Agras, by Wellcome Principal Fellowship, grant 046389 to Dr. Fairburn, and by Eli Lilly & Co.	BE/week; PE/week, BDI, EDE, RSES	Fluoxetine may be a practical intervention for patients with bulimia nervosa who have not responded adequately to psychological treatment.
Walsh et al., 2004 (Leombruni et al., 2008)	Outpatients *N* = 49	Age: 31 F: 100 %	DSM-IV SCID	16 weeks; open-label	Fluoxetine (60 mg/day)	Placebo	Supported in part by the National Institute of Diabetes and Digestive and Kidney Diseases grant DK-53635. Dr. Fairburn is supported by a Principal Research Fellowship from the Wellcome Trust (046386)	BE/week; PE/week; days of vomiting/month; BDI; SCL-53	Treatment with fluoxetine is associated with better retention and substantial symptomatic improvement compared to placebo.

Legend: FBNCSG: Fluoxetine Bulimia Nervosa Collaborative Study Group; DSM: Diagnostic and Statistical Manual for mental disorders; DH: Day Hospital; SCID: Structured Clinical Interview for DSM; BMI: Body Mass Index; SIABN: Structured Interview for Anorexia and Bulimia Nervosa; rTMS: repetitive Transcranial Magnetic Stimulation; CBT: Cognitive-Behavioral Therapy; iCBT: intensive-Cognitive-Behavioral Therapy; BE: Binge Episode; PE: Purging Episode; MADRS: Montgomery-Åsberg Depression Rating Scale; EDI (-2): Eating Disorder Inventory (2); HDRS: Hamilton Depression Rating Scale; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; BDI: Beck Depression Inventory; (H)SCL-90/53: (Hopkins) Symptom Checklist-90/53; HRQOL: Health-Related Quality of Life; TFEQ: Three-Factor Eating Questionnaire; EDE (Q): Eating Disorder Examination (Questionnaire); EAT: Eating Attitude Test; BITE: Bulimic Investigatory Test; CGI: Clinical Global Inventory; HARS: Hamilton Anxiety Rating Scale; STAI: State-Trait Anxiety Inventory. NIMH: National Institute of Mental Health. NIH: National Institute of Health.

and desipramine 300 mg/day vs. placebo (Walsh et al., 1991) led to a significant reduction of BEs frequency besides improvement in depressive symptomatology.

The serotonin, norepinephrine, dopamine enzyme inhibitor (SNDEI) brofaromine significantly reduced PEs and weight loss, although associated with marked side effects vs. placebo (Kennedy et al., 1993). On the contrary, the SNDEI moclobemide demonstrated an overall safety profile but was ineffective in reducing BEs and PEs (Carruba et al., 2001).

Finally, trazodone 300 mg/day failed to outperform the placebo in BN patients (Pope Jr. et al., 1989).

3.2.1.1. Meta-analysis of fluoxetine treatment vs. placebo. Ten studies (Beumont et al., 1997; Fichter et al., 1991; Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992; Goldbloom et al., 1997; Goldstein et al., 1995; Kanerva, 1995; Mitchell et al., 2001; Romano et al., 2002; Walsh et al., 2000; Walsh et al., 2004) provided quantitative data about fluoxetine vs. placebo, encompassing a total of 1383 patients, mean age = 27 years, of whom 99.5 % were females. The average duration of the RCTs was 15 weeks, while the mean dose of fluoxetine was 60 mg/day. Only one RCT employed fluoxetine 20 mg/day in one of the three arms (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992). One RCT also used intensive behavioral psychotherapy for the included inpatients (Fichter et al., 1991).

Five studies fetching six comparisons (Beumont et al., 1997; Fichter et al., 1991; Mitchell et al., 2001; Romano et al., 2002; Walsh et al., 2004) considered the reduction of BEs frequency: Hedges'g = 0.203 (95%C.I. = 0.007–0.399), I^2 = 0 %; p = .042 (Supplementary Fig. 23). No publication bias was detected: *Egger test*: *beta* = 0.817 (p = .671) (Supplementary Fig. 24).

Three RCTs fetching four comparisons (Mitchell et al., 2001; Romano et al., 2002; Walsh et al., 2004) considered the reduction of PEs frequency: Hedges'g = 0.328 (95%C.I. = −0.061–0.717), I^2 = 58.97 %; p = .099 (Supplementary Fig. 25). No publication bias detected: *Egger test*: *beta* = 3.713 (p = .229) (Supplementary Fig. 26).

Four RCTs fetching four comparisons considered weight change (Fichter et al., 1991; Kanerva, 1995; Walsh et al., 2000; Walsh et al., 2004): Hedges'g = 0.147 (95%C.I. = −0.157–0.451), I^2 = 0 %; p = .343 (Supplementary Fig. 27). No publication bias was detected: *Egger test*: *beta* = −1.168 (p = .574) (Supplementary Fig. 28).

Four studies fetching four comparisons considered the reduction of the total score on ED-specific rating scales, namely the EDI and the EDE (Beumont et al., 1997; Kanerva, 1995; Romano et al., 2002; Walsh et al., 2000): Hedges'g = 0.488 (95%C.I. = 0.128–0.849), I^2 = 50.02 %; p = .008 (Supplementary Fig. 29). No publication bias was detected: *Egger test*: *beta* = 1.345 (p = .646) (Supplementary Fig. 30).

Five studies fetching five comparisons (Beumont et al., 1997; Fichter et al., 1991; Romano et al., 2002; Walsh et al., 2000; Walsh et al., 2004) considered the reduction of the total score on rating scales for depressive symptomatology, namely the BDI and the HDRS: Hedges'g = 0.331 (95%C.I. = 0.115–0.547), I^2 = 0 %; p = .003 (Supplementary Fig. 31). No publication bias was detected: *Egger test*: *beta* = 1.883 (p = .109) (Supplementary Fig. 32).

3.2.1.2. Sub-group analysis of fluoxetine treatment vs. placebo. No subgroup analyses could be performed for PEs frequency and ED-specific psychopathology because the relevant studies did not account for concurrent psychotherapy.

3.2.1.3. Meta-regression of fluoxetine treatment vs. placebo. The longer the trial duration, the lower the reduction of PEs (beta = −0.014, 95%C.I. = 0.026 to −0.001, R^2 = 0, p = .036, k = 3, comparisons = 4) (Supplementary Fig. 33).

Although failing to reach statistical significance, a trend of lesser efficacy in improving ED-specific psychopathology, according to adopted rating scales, was observed with a longer trial duration (Supplementary Fig. 34).

3.2.2. Other pharmacological treatment options

Topiramate was evaluated in one RCT (Nickel et al., 2005), showing good tolerability and efficacy in reducing BEs/PEs frequency, decreasing weight, and improving the perceived quality of life.

Ondansetron reduced PEs and their duration, besides BEs (Faris et al., 2000).

According to one RCT, d-fenfluramine failed to benefit patients with BN (Fahy et al., 1993). Finally, naltrexone, compared vs. a placebo, improved depressive symptomatology and reduced the duration of BEs, although not affecting their frequency (Alger et al., 1991).

3.3. Pharmacological treatment for binge eating disorder

Seventeen RCTs (Appolinario et al., 2003; Brambilla et al., 2009; Grant et al., 2019; Grilo et al., 2021; Grilo et al., 2005; Guerdjikova et al., 2009; Guerdjikova et al., 2012; Guerdjikova et al., 2016; Hudson et al., 1998; Leombruni et al., 2008; McElroy et al., 2003; McElroy et al., 2000; McElroy et al., 2015a; McElroy et al., 2007; McElroy et al., 2015b; Pearlstein et al., 2003; Ricca et al., 2001) encompassing 2343 patients dealt with BED fetched 23 comparisons. The publication range of the studies was 1998–2001. Please refer to Table 3 for details. The primary outcomes considered were weight loss, usually recorded as a BMI variation, frequency of BEs per week, and the days of binging per week (number of days with at least one BE within a week).

Several RCTs considered the change in the score of different psychometric measures, as detailed in Table 3. ED-specific psychopathology was assessed using either the EDE, the EDE-Q, the EDI, the EDI-2, the TFEQ, or the BES. Depressive symptomatology was rated using the HDRS, the BDI, or the MADRS. Obsessive-compulsive symptomatology was explored using the Y-BOCS or the Y-BCEDS.

Remission, defined by the authors as BEs cessation within 28 days before the conclusion of the study, was assessed by five RCTs (Grilo et al., 2005; Guerdjikova et al., 2009; Guerdjikova et al., 2016; Hudson et al., 1998; McElroy et al., 2007). In addition, two studies reported data on remission, defined by the author as 4-week BEs cessation (McElroy et al., 2015a; McElroy et al., 2015b).

Most of the studies compared an active treatment vs. placebo. Only one RCT included two active treatment arms: fluoxetine and sertraline (Leombruni et al., 2008). The active treatment plus CBT was compared against CBT alone in 2 RCTs (Grilo et al., 2005; Ricca et al., 2001). Please refer to Table 3 for details.

3.3.1. Amphetamine derivatives treatment

Lisdexamfetamine was evaluated in 3 RCTs (Guerdjikova et al., 2016; McElroy et al., 2015a; McElroy et al., 2015b). In addition, one record documented two different multicentric RCTs, named "study 1" and "study 2" (McElroy et al., 2015a). Overall, the mean dose = 54.02 mg/day (range 30-70 mg/day). Adverse events (AEs) were common: dry mouth, insomnia, headache, and anxiety; however, lisdexamfetamine significantly reduced weight and BEs frequency. Overall, lisdexamfetamine failed to provide any benefit for depressive (McElroy et al., 2015b) or obsessive-compulsive symptomatology (Guerdjikova et al., 2016; McElroy et al., 2015a; McElroy et al., 2015b).

One RCT included three active treatment arms (lisdexamfetamine 30, 50, and 70 mg/day) vs. placebo (McElroy et al., 2015b). Only lisdexamfetamine 30 mg/day failed to outperform the placebo (McElroy et al., 2015b). Lisdexamfetamine 50 mg/day significantly improved general and specific ED psychopathology and 4-week BEs cessation (McElroy et al., 2015b).

Sibutramine 15 mg/day was evaluated in a 12-week RCT (Appolinario et al., 2003), showing good tolerability and significant efficacy in reducing BEs frequency, weight, and total score of the BDI.

3.3.1.1. Meta-analysis of lisdexamfetamine treatment vs. placebo. Three RCTs (Guerdjikova et al., 2016; McElroy et al., 2015a; McElroy et al., 2015b) fetching six comparisons provided quantitative data about lisdexamfetamine vs. placebo, encompassing a total of 1049 patients, mean age = 38 years (range 37.7–38.7), of whom 84 % were females. The duration of the RCTs ranged from 11 (McElroy et al., 2015b) to 12 weeks (Guerdjikova et al., 2016; McElroy et al., 2015a), while the mean dose of fluoxetine was 56.02 mg/day (range 30-70 mg/day)—none of the three studies involved psychotherapy.

The Hedges'g ' weight loss, in terms of BMI (Guerdjikova et al., 2016) or body weight change (McElroy et al., 2015b), was 0.259 (95%C.I. = 0.071–0.446), $I^2 = 0$ %; $p = .007$, based on k = 2, comparisons = 4 (Supplementary Fig. 35). No publication bias was detected: *Egger test*: *beta* = −1.057 ($p = .475$) (Supplementary Fig. 36).

The Hedges'g for the reduction of BEs frequency was 0.571 (95%C.I. = 0.282–0.860), $I^2 = 53.84$ %; $p < .001$, based on k = 2, comparisons = 4 (Guerdjikova et al., 2016; McElroy et al., 2015b) (Supplementary Fig. 37). No publication bias was detected: *Egger test*: *beta* = 5.642 ($p = .145$) (Supplementary Fig. 38).

The Hedges'g for the reduction of days of binging per week was 1.028 (95%C.I. = 0.589–1.467), $I^2 = 91.17$ %; p < .001, based on k = 3, comparisons = 6 (Guerdjikova et al., 2016; McElroy et al., 2015a; McElroy et al., 2015b) (Supplementary Fig. 39). No publication bias was detected: *Egger test*: *beta* = −7.477 ($p = .124$) (Supplementary Fig. 40).

The Hedges'g for specific ED psychopathology, assessed through the BES or the TFEQ, was = 0.764 (95%C.I. = 0.474–1.054), $I^2 = 53.01$ %; p < .001, based on k = 2, comparisons = 4 (Guerdjikova et al., 2016; McElroy et al., 2015b) (Supplementary Fig. 41). No publication bias was detected: *Egger test*: *beta* = −1.756 ($p = .767$) (Supplementary Fig. 42).

The Hedges'g for the reduction of depressive symptomatology, assessed through the MADRS in a 3-arm RCT (McElroy et al., 2015b), was 0.074 (95%C.I. = −0.124–0.273), $I^2 = 0$ %; $p = .463$, based on k = 1, comparisons = 3 (Supplementary Fig. 43). No publication bias was detected: *Egger test*: *beta* = 40.985 ($p = .781$) (Supplementary Fig. 44).

The Hedges'g for the reduction of obsessive-compulsive symptomatology, assessed through the Y-BOCS in the 3 RCTs, was 1.249 (95%C.I. = 0.612–1.886), $I^2 = 95.44$ %; p < .001, based on k = 3, comparisons = 6 (Guerdjikova et al., 2016; McElroy et al., 2015a; McElroy et al., 2015b) (Supplementary Fig. 45). Statistically significant publication bias was detected: *Egger test*: *beta* = −15.143 ($p = .027$), although Duval and Tweedie's trim analysis was not significant. The pooled Hedges'g was unadjusted (Supplementary Fig. 46).

3.3.1.2. Subgroup analysis of lisdexamfetamine treatment vs. placebo. No subgroup analyses could be performed for ED-specific psychopathology and BE frequency due to the lack of relevant studies assessing concurrent CBT.

3.3.1.3. Meta-regression of lisdexamfetamine treatment vs. placebo. A higher mean dose of lisdexamfetamine predicted lower scores in BED psychopathological measures, beta = 0.013, 95%C.I. = 0–0.025, $R^2 = 0.001$, $p = .039$, based on k = 2, comparisons = 4 (Guerdjikova et al., 2016; McElroy et al., 2015b) (Supplementary Fig. 47).

Although failing to reach statistical significance, meta-regression showed a trend for improvement in BE frequency and days of binging per week as the mean dose of lisdexamfetamine increased, based on k = 2, comparisons = 4 (Supplementary Fig. 48), and k = 3, comparisons = 6 (Guerdjikova et al., 2016; McElroy et al., 2015a; McElroy et al., 2015b) (Supplementary Fig. 49), respectively.

3.3.2. Antidepressant treatment

Vortioxetine 20 mg/day failed to outperform the placebo (Grant et al., 2019). Duloxetine at a mean dose = 78.9 mg/day helped reduce BE frequency, although not differing from placebo in improving BMI, ED-specific psychopathology, anxiety, and depression (Guerdjikova et al., 2012).

Bupropion 300 mg/day plus naltrexone 50 mg/day was evaluated in a 12-week RCT (Grilo et al., 2021), showing no significant results compared to placebo.

Fluvoxamine at a mean dose = 250 mg/day was compared to a placebo in 2 RCTs (Hudson et al., 1998; Pearlstein et al., 2003). Only one study (Hudson et al., 1998) significantly reduced BE frequency, weight, and overall psychopathological symptoms. Fluvoxamine plus intensive CBT failed to provide any advantage compared to intensive CBT alone (Ricca et al., 2001). Concordantly, fluoxetine 60 mg/day failed to provide any significant benefit in addition to CBT or placebo, against placebo alone or CBT alone (Grilo et al., 2005).

One 6-month study compared fluoxetine (mean dose = 55 mg/day) vs. sertraline (mean dose = 150 mg/day), showing a significant improvement in the BES score and significant weight loss after eight weeks for both treatment arms, an effect the responders maintained up to the completion of the trial (Leombruni et al., 2008).

Sertraline outperformed placebo in reducing BE frequency, weight, and general psychopathological symptoms (McElroy et al., 2000).

3.3.3. Anticonvulsant treatment

Sertraline 150 mg/day monotherapy improved depressive symptoms and the quality of the interpersonal relationship. Its augmentation with topiramate 150 mg/day also significantly reduced EDs specific psychopathology and weight; both treatment arms involved women receiving concurrent CBT and dietary indications (Brambilla et al., 2009).

Topiramate was evaluated vs. placebo in 2 RCTs, showing efficacy in reducing BE frequency, weight, and general and ED-specific psychopathology at a mean dose of 212 (McElroy et al., 2003) and 300 mg/day (McElroy et al., 2007) respectively. Topiramate showed good tolerability overall, although associated with paresthesia, dry mouth, headache, dyspepsia, dizziness, and drowsiness (McElroy et al., 2003).

Lamotrigine at a mean dose = 236 mg/day led to significant weight loss vs. placebo in a 16-week RCT (Guerdjikova et al., 2009).

4. Discussion

The present SR and MA (Cassioli et al., 2020; Han et al., 2022; Treasure et al., 2015) is a primer as it concurrently appraises standard weight and "affective" psychopathology in the broadest sense, including depressive and anxiety-related outcomes relevant to the psychopharmacology of different EDs.

4.1. Main findings: pharmacological treatment of anorexia nervosa

Compared to the most current quantitative report on the matter (Cassioli et al., 2020), the present one also included additional records for fluoxetine for non-acute phases of AN (Kaye et al., 2001; Walsh et al., 2006), SNMAs (Brambilla et al., 1995b, 1995c), and the cannabinoid dronabinol (Andries et al., 2014). Interestingly, the present MA allowed for an additional RCT on olanzapine (Attia et al., 2019) indexed upon competition of the most current previous report (Cassioli et al., 2020). Specifically, the study involved 152 patients, representing a substantially large sample size among the herein pooled AN studies. Sensitivity analyses indicated that the inclusion of the 2019 report (Attia et al., 2019) shifted the Hedges'g for BMI from 0.353 (C.I. = 0.013 to 0.693) to 0.283 (C.I. = 0.051–0.515) and the Hedges'g for obsessive-compulsive psychopathology from 0.359 (C.I. = −0.055 to 0.774) to 0.171 (C.I. = 0.113–0.455), suggesting a trend for increased effect on weight gain and a reduced effect on obsessive symptoms for olanzapine among people with AN compared previous meta-analytic report (Cassioli et al., 2020), though none of the effect sizes reached a statistically significant threshold. Weight gain with olanzapine represents a quite anticipated finding in the clinical practice, confirmed by a recent MA in AN patients (Cassioli et al., 2020). This is a core issue considering that they often endorse the drive for thinness (Treasure et al., 2015). Forthcoming

Table 3
Qualitative analysis of psychopharmacological treatment in binge-eating disorder: 17 original studies fetched 23 comparisons.

Binge eating disorder									
Authors, year	Population; N = sample size	Mean age (years) Female %	Diagnosis DSM/ICD and type of interview	Duration of the trial and design	Active treatment (Mean dose)	Control group	Sponsorship	Main outcomes	Main findings
Appolinario et al., 2003 (McElroy et al., 2000)	Outpatients *N* = 60	Age: 36 F: 88 %	DSM-IV SCID	12 weeks	Sibutramine (15 mg/day)	Placebo	Supported by the Abbott Laboratories do Brasil Ltda, Sao Paulo, Brazil	Days of Binge, weight, BES, BDI	Sibutramine is effective and well-tolerated in treating obese patients with BED (its effects address binge-eating episodes, weight, and depressive symptoms).
Brambilla et al., 2009 (McElroy et al., 2003)	Outpatients *N* = 20	Age: 47 F: 100 %	DSM-IV SCID	Six months	Sertraline+topiramate (150 + 150 mg/day) + CBT + diet	CBT + diet	No info	BE/week; weight, BMI, EDI-2, SCL-90; PDQ-4-R	Binge frequency and weight decreased in cases in whom improvement was noted in total EDI-2 and SCL-90-R scores. Combination therapy seems to be the only highly effective treatment for BED patients. Binge frequency and excessive weight don't decrease in cases in whom improvement was noted only on the SCL-90-R subitems "depression" and "interpersonal relationship."
Brambilla et al., 2009 (McElroy et al., 2015b)	Outpatients N = 20	Age: 46 F: 100 %	DSM-IV SCID	Six months	Sertraline (150 mg/day) + CBT + diet	CBT + diet			
Grant et al., 2019 (McElroy et al., 2015b)	Outpatients *N* = 80	Age: 40 F: 67 %	DSM-5 MINI	12 weeks	Vortioxetine (20 mg/day)	Placebo	Funded by an investigator-initiated research grant from Takeda Pharmaceuticals to Dr. Grant	BE/week, weight, BMI	Vortioxetine and placebo were associated with a significant reduction in binge-eating frequency. But vortioxetine group significantly differed from the placebo on any efficacy measure.
Grilo et al., 2005 (McElroy et al., 2015b)	Outpatients *N* = 54	Age: 44 F: 78 %	DSM-IV SCID	16 weeks	Fluoxetine (60 mg/day)	Placebo	She was supported by grant DK49587 from the NIH to Grilo C.M.	Remission rate, EDEQ, BE/week, TFEQ, BDI	The findings demonstrated the efficacy of CBT, but not fluoxetine, for BED's behavioral and psychological features. Fluoxetine was not superior to placebo, and CBT plus placebo and CBT plus fluoxetine did not differ. In contrast, CBT plus placebo and CBT plus fluoxetine were significantly superior to fluoxetine-only and placebo-only.
Grilo et al., 2005 (McElroy et al., 2015a)	Outpatients N = 54	Age: 44 F: 78 %	DSM-IV SCID	16 weeks	Fluoxetine (60 mg/day) + CBT	Placebo+CBT			
Grilo et al., 2021 (McElroy et al., 2015a)	Outpatients N = 22	Age: 50 F: 86 %	DSM-5 MINI	12 weeks	Naltrexone+bupropion (50 + 300 mg/day)	Placebo	Supported, in part, by NIH grants.	BE/week, BMI, weight, BDI, EDE	Reduction from baseline in binge-eating episodes, eating disorder psychopathology depression, and weight during treatment in the Naltrexone/ Bupropion combination group,

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Table 3 (*continued*)

Binge eating disorder									
Authors, year	Population; N = sample size	Mean age (years) Female %	Diagnosis DSM/ICD and type of interview	Duration of the trial and design	Active treatment (Mean dose)	Control group	Sponsorship	Main outcomes	Main findings
									but not significantly from the placebo group.
Guerdjikova et al., 2009 (McElroy et al., 2007)	Outpatients *N* = 51	Age: 44 F: 77 %	DSM-IV SCID	16 weeks	Lamotrigine (236 mg/day)	Placebo	Supported in part by a grant from GlaxoSmithKline	Days of a binge; BE (mean change); remission rate, BMI, HDRS, CGI, Y-BOCS	Lamotrigine and placebo had similar rates of reduced weekly frequency of binge-eating episodes and binge days, weight, and BMI. However, Lamotrigine was associated with a numerically greater amount of weight loss. The study had an exceptionally high placebo response.
Guerdjikova et al., 2012 (Pearlstein et al., 2003)	Outpatients. N = 40	Age: 40 F: 88 %	DSM-IV SCID	12 weeks	Duloxetine (78.7 mg/day)	Placebo	Supported in part by a grant from Eli Lilly	BE/week; weight, BMI	Duloxetine outperformed placebo in reducing the weekly frequency of binge eating days and BE. Changes in BMI, measures of eating pathology, depression, and anxiety did not differ between the two groups.
Guerdjikova et al., 2016 (Ricca et al., 2001)	Outpatients *N* = 50	Age: 38 F: 92 %	DSM-IV SCID	12 weeks	Lisdexamfetamine (59.6 mg/day)	Placebo	Supported by a grant from Shire.	Days of a binge, BE/ week; remission rate; BMI, TFEQ, Y-BOCS-BE, CGI	Lisdexamfetamine was not associated with a significantly higher remission rate (cessation of binge in 4-week). Still, it was associated with a significantly decreased weight, BMI, BE days/week, and BE episodes/ week. Side effects were quite common in the lisdexamfetamine group. The most common were dry mouth, jitteriness, and insomnia.
Hudson et al., 1998 (Ricca et al., 2001)	Outpatients *N* = 85	Age: 42 F: 91 %	DSM-IV clinical diagnosis	Nine weeks	Fluvoxamine (260 mg/day)	Placebo	Supported in part by a grant from the Upjohn Co. and Solvay Pharmaceuticals	BE/week (log); remission rate HDRS, CGI, BMI	Compared with placebo, fluvoxamine was associated with a significantly greater rate of reduction in the frequency of binges, rate of decrease in CGI scores, and BMI. However, a significant proportion of patients receiving placebo discontinued treatment because of adverse events.
Leombruni et al., 2008 (Pearlstein et al., 2003)	Outpatients *N* = 42	Age: 40 F: 100 %	DSM-IV SCID	24 weeks	Fluoxetine (40-80 mg/day)	Sertraline (100–200 mg/day)	No info	BE/week; weight, BMI, CGI, BES, BDI	After eight weeks of treatment, a significant improvement in the BES score and

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Table 3 (*continued*)

Binge eating disorder									
Authors, year	Population; N = sample size	Mean age (years) Female %	Diagnosis DSM/ICD and type of interview	Duration of the trial and design	Active treatment (Mean dose)	Control group	Sponsorship	Main outcomes	Main findings
									considerable weight loss emerged. These results were maintained by responders (weight loss of at least 5 % of baseline weight) over 24 weeks. A 6-month treatment with SSRI may be a practical option.
McElroy et al., 2000 (Ricca et al., 2001)	Outpatients *N* = 34	Age: 42 F: 94 %	DSM-IV clinical diagnosis	Six weeks	Sertraline (187 mg/day)	Placebo	Supported in part by a grant from Pfizer	BE/week (log); HDRS, CGI, BMI	Compared with placebo, sertraline was associated with a significantly greater rate of reduction in the frequency of binges, rate of decrease in CGI scores, and BMI. Sertraline was effective and well-tolerated.
(Ricca et al., 2001)	Outpatients *N* = 61	Age: 41 F: 87 %	DSM-IV clinical diagnosis	14 weeks	Topiramate (212 mg/day)	Placebo	Supported in part by funding from Ortho McNeil Pharmaceutical	BE/week (log); BMI, remission rate, HDRS, CGI, Y-BOCS	Compared with placebo, topiramate was associated with a significantly greater rate of reduction in binge frequency, binge day frequency, BMI, weight, and CGI and Y-BOCS scores. Topiramate was efficacious and relatively well tolerated.
McElroy et al., 2015a (Pearlstein et al., 2003)	Outpatients *N* = 129	Age: 39 F: 82 %	DSM-IV SCID	11 weeks	Lisdexamfetamine (30 mg/day)	Placebo	Supported by Shire Development, LLC.	Days of a binge; BE (mean change); 4-weeks-BE-cessation, HARS, CGI, BES, Y-BOCS-BE, MADRS, BIS-11.	In the present Phase 2 trial, the 30 mg treatment group did not demonstrate efficacy compared to the placebo group.
McElroy et al., 2015a (Ricca et al., 2001)	Outpatients *N* = 128	Age: 39 F: 77 %	DSM-IV SCID	11 weeks	Lisdexamfetamine (50 mg/day)	Placebo			The 50 mg treatment group demonstrated efficacy compared with the placebo group in decreasing BE days, remission rate, and global improvement (CGI).
McElroy et al., 2015a (Ricca et al., 2001)	Outpatients N = 128	Age: 39 F: 81 %	DSM-IV SCID	11 weeks	Lisdexamfetamine (70 mg/day)	Placebo			The 70 mg treatment group demonstrated efficacy compared with the placebo group in reducing BE days, remission rate, and global improvement (CGI). Adverse events were common (84,7 % in LDX and 54,7 % in the placebo group), primarily dry mouth and insomnia.
McElroy et al., 2015b (Pearlstein et al., 2003)	Outpatients *N* = 383	Age: 38 F: 87 %	DSM-IV SCID	12 weeks	Lisdexamfetamine (56.9 mg/day)	Placebo	The sponsor, Shire Development LLC, funded clinical research.	Days of a binge; BE (mean change); 4-weeks-BE-cessation,	In the present Phase 3 trials, lisdexamfetamine was superior to placebo in decreasing binge eating days/

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Table 3 (*continued*)

Binge eating disorder									
Authors, year	Population; N = sample size	Mean age (years) Female %	Diagnosis DSM/ICD and type of interview	Duration of the trial and design	Active treatment (Mean dose)	Control group	Sponsorship	Main outcomes	Main findings
McElroy et al., 2015b (Ricca et al., 2001)	Outpatients *N* = 390	Age: 38 F: 85 %	DSM-IV SCID	12 weeks	Lisdexamfetamine (57.6 mg/day)	Placebo		CGI, Y-BCEDS, side effects	week from baseline and improving binge eating-related key secondary endpoints. However, headache, insomnia, and dry mouth were the most frequently reported side effects of lisdexamfetamine in each study.
McElroy et al., 2007 (Ricca et al., 2001)	Outpatients *N* = 407	Age: 44 F: 84 %	DSM-IV SCID	16 weeks	Topiramate (300 mg/day)	Placebo	Sponsored by Ortho-McNeil Neurologic, Titusville, New Jersey.	Days of a binge; BE (mean change); remission rate, BMI, HDRS, CGI, Y-BOCS	Topiramate-induced binge-eating remission in 58 % of patients (placebo 29 %) was well tolerated and efficacious in improving the features of BED and in reducing obesity.
Pearlstein et al., 2003 (Pearlstein et al., 2003)	Outpatients N = 20	Age: 41 F: 85 %	DSM-IV SCID	12 weeks	Fluvoxamine (239 mg/day)	Placebo	Supported in part by a grant from Solvay Pharmaceuticals.	Days of Binge, EDE-Q, BDI, HDRS; CGI	There were no significant differences between fluvoxamine and placebo for any treatment outcome variables.
Ricca et al., 2001 (Ricca et al., 2001)	Outpatients N = 42	Age: 26 F: 62 %	DSM-IV Semi-structured interview	24 weeks; open label	Fluoxetine (20-60 mg/day) + CBT	CBT only	No info	Days of Binge, BMI, EDE, STAI, BDI, EDEQ	CBT was more effective than fluoxetine in the treatment of BED.
Ricca et al., 2001 (Ricca et al., 2001)	Outpatients N = 43	Age: 26 F: 60 %	DSM-IV Semi-structured interview	24 weeks; open label	Fluvoxamine (100-300 mg/day) + CBT	CBT only			Adding fluoxetine to CBT does not seem to provide any clear advantage on eating behaviors. CBT was more effective than fluvoxamine in the treatment of BED. Adding fluvoxamine to CBT does not seem to provide any clear advantage on eating behaviors.

Legend: DSM: Diagnostic and Statistical Manual for mental disorders; DH: Day Hospital; SCID: Structured Clinical Interview for DSM; BMI: Body Mass Index; MINI: Mini-International Neuropsychiatric Interview version 7.0; CBT: Cognitive-Behavioral Therapy; BE: Binge Episode; EDE (Q): Eating Disorder Examination (Questionnaire); EDI (-2): Eating Disorder Inventory (2); HDRS: Hamilton Depression Rating Scale; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; BDI: Beck Depression Inventory; PDQ-4-R: Personality Diagnostic Questionnaire-4-Revision; CGI: Clinical Global Inventory; MADRS: Montgomery-Asberg Depression Rating Scale; HARS: Hamilton Anxiety Rating Scale; BIS-11: Barratt Impulsiveness Scale; SCL-90: Symptom Checklist-90; BES: Binge Eating Scale; STAI: State-Trait Anxiety Inventory; TFEQ: Three-Factor Eating Questionnaire; Y-BCEDS: Yale-Brown Cornell Eating Disorder Scale. NIMH: National Institute of Mental Health. NIH: National Institute of Health.

studies should also record metabolic parameters over extended follow-up periods, especially considering that the sole weight restoration does not account for the general health status nor the complexity of the clinical psychopathology of AN or other EDs.

Additional insight into the efficacy of psychotherapy augmentation for pharmacotherapy in AN are warranted. The most current UR on different mental disorders, including EDs, excluded augmentation strategies, documenting only a marginal benefit of psychological monotherapy in AN compared to TAU or placebo: standardized mean differences (SMDs) = 0.10 and 0.31; risk ratios = 0.97 and 1.28, respectively, as well as pharmacological monotherapy (SMD = 0.25) (Leichsenring et al., 2022).

In line with previous evidence (Cassioli et al., 2020), the present report failed to detect any statistically significant difference in ED, depressive, anxious, and obsessive-compulsive symptomatology, thus excluding a beneficial effect of olanzapine vs. placebo.

The present MA represents the first piece to document quantitative synthesis about fluoxetine vs. placebo for people with a primary diagnosis of AN, concurrently appraising weight and depressive and obsessive-compulsive outcomes. Especially, weight gain failed to reach a statistically significant threshold according to the three pooled studies lasting 52 (Kaye et al., 2001; Walsh et al., 2006) and seven weeks (Attia et al., 1998), respectively. Furthermore, higher doses of fluoxetine statistically significantly predicted a lower propensity for weight gain. This may appear an unexpected outcome, especially considering that fluoxetine features the highest post-synaptic 5-HT_{2C} antagonism in the SSRI

class (Ni and Miledi, 1997). However, chances are that at least some AN patients may experience mood excitement with high doses of fluoxetine, leading to starvation, at least in the acute setting, even in the absence of a conclusive diagnosis of full-threshold major depression or bipolar disorder comorbidity (Fornaro et al., 2021). Sub-group analysis also highlighted a statistically significant weight gain with fluoxetine over placebo for the sole AN-R against non-specified subtype AN (Kaye et al., 2001).

4.2. Main findings: pharmacological treatment of bulimia nervosa

Fluoxetine trials were the only ones allowing quantitative synthesis concerning the antidepressant treatment of BN. Fluoxetine outperformed placebo monotherapy, except for one trial, including inpatients receiving intensive psychotherapy and placebo controls also receiving intensive psychotherapy (Fichter et al., 1991). This issue may have hindered the efficacy of the active intervention, even concerning depressive psychopathology. The results of a three-arm 16-week RCT involving fluoxetine 60 mg/day vs. fluoxetine 60 mg/day plus weekly CBT vs. weekly CBT alone also demonstrated that CBT monotherapy led to better outcomes than CBT plus fluoxetine, which in turn resulted slightly more effective than fluoxetine monotherapy (Goldbloom et al., 1997). However, it must be remarked that fluoxetine monotherapy was beneficial for those patients who had already failed to improve with sole psychotherapy intervention (Walsh et al., 2000). The assessed RCTs did not account for personality disorders or traits, despite their influence on psychotherapy outcomes (Simpson et al., 2022). In addition, uncertainty exists about the long-term efficacy of fluoxetine in the management of PEs associated with BN since the pertaining exploratory meta-regression analysis could include only two 16-week trials (Mitchell et al., 2001; Walsh et al., 2004) and a 52-week study (Romano et al., 2002), and the latter one-year study was also the only one documenting lower efficacy of fluoxetine compared to the other twos. Fluvoxamine proved effective in the prevention of relapse of BN (Fichter et al., 1997) and the reduction of the BITE score (Brambilla et al., 1995a), rather than depressive, anxiety, and body image psychopathology (Fichter et al., 1997) or EDI score (Brambilla et al., 1995a).

The evidence about different SNMAs and SNDEIs is sparse. Similarly, the appraised evidence for topiramate, naloxone, and ondansetron relied on a handful of trials, precluding firm conclusions.

4.3. Main findings: pharmacological treatment of binge eating disorder

Compared to the existing meta-analysis literature (Hilbert et al., 2020), the present SR and MA include two recently appraised RCTs (Grant et al., 2019; Grilo et al., 2021).

Three studies were included in the meta-analytic synthesis of BED results concerning lisdexamfetamine (Guerdjikova et al., 2016; McElroy et al., 2015a; McElroy et al., 2015b). Lisdexamfetamine proved effective for binging but not for depressive psychopathology, and a higher mean dose predicted lower scores in BED psychopathology measures, according to exploratory meta-regression analysis; this finding solicits additional primary studies on the matter to shed further light also on the safety profile of the drug vs. placebo or other active compounds. In addition, the "remission" outcome was substantially underreported by the appraised BED studies, as in AN and BN trials. Among other implications, the definition of remission remains elusive, especially for BED, essentially relying on the cessation of BEs lasting for at least four weeks preceding the endpoint evaluation (Grilo et al., 2005; Guerdjikova et al., 2009; Guerdjikova et al., 2016; Hudson et al., 1998; McElroy et al., 2007).

Unsurprisingly, the present SR and MA could provide sufficient quantitative information only for lisdexamfetamine because the latter represents the only drug approved by the FDA to date. Alternative pharmacological treatments appraised in the qualitative synthesis of the present report nonetheless solicit additional primary studies, including people with a primary diagnosis of BED.

4.4. Limitations of the study

The limitations of the present study essentially rely on the sample size, duration, and operational definitions adopted by the included RCTs. Sponsorship and publication biases may have precluded additional analyses for most recently introduced compounds. Finally, prudence is warranted in interpreting the results from exploratory meta-regression analyses when relying on a limited number of studies. Finally, no network meta-analysis was carried out currently since most comparisons relied on a handful of active interventions vs. placebo, thus precluding indirect comparisons.

5. Conclusions

Forthcoming studies should provide reliable operational definitions for "remission" across different EDs. Specifically, the herein appraised authors' definitions often relied on weight change or strictly related outcomes over short follow-up periods, underscoring the clinical relevance of broad metabolic and "affective" psychopathology records.

EDs are often comorbid with other psychiatric disorders, such as bipolar disorder (Fornaro et al., 2021), also prompting attention to different interventions and therapeutic outcomes by forthcoming primary studies. This is compelling considering the undisputed efficacy of psychotherapy for people with EDs and the high attrition rates leading to underpowered trials documented for those studies comparing pharmacological treatment augmented with psychotherapy vs. psychotherapy alone, despite most of the included studies being rated high-quality overall. Finally, the included RCTs barely accounted for acceptability outcomes, nonetheless outlined in the qualitative tables whenever disclosed, reinforcing the plea for high-quality primary research on the psychopharmacology of EDs, with a particular emphasis on their "affective" core.

CRediT authorship contribution statement

Contributors: Drs: MF, AMM, and AF conceived the study. MB, MDP and CC put significant efforts into reviewing the statistical analyses and overall procedures. FM, RC, AFC and AdB either served as senior reviewers or they critically appraised the results of the study.

Funding sources

There is none to disclose in conjunction with present piece of work.

Declaration of competing interest

None of the authors has any conflict of interest whatsoever to disclose in conjunction with the present rereport.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.06.068.

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