

REVIEW ARTICLE

The efficacy of antidepressant therapy on obesity: A systematic review

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Abstract

Antidepressant medications variably affect weight and metabolic outcomes and pose risks related to obesity. The clinical relevance of these effects across randomized trials remains unclear. Understanding these effects can inform treatment selection for patients with obesity. Relevant studies were identified through searches of PubMed, MEDLINE, Cochrane Library, Web of Science, PsycINFO, Scopus, and Embase. Studies were included if they were randomized controlled trials reporting whether a Food and Drug Administration-approved antidepressant agent was associated with obesity-related measures as either a primary outcome, secondary outcome, or safety outcome. Of the 222 identified records, 19 eligible studies (all randomized controlled trials, comprising 24,256 participants) met the inclusion criteria. In trials that combined pharmacotherapy with behavioral/psychotherapeutic interventions, fluoxetine was associated with larger weight reductions (−7.89 kg with fluoxetine + metformin vs. −0.48 kg in a comparator group in one trial), and cognitive behavioral therapy + fluoxetine produced greater reductions in binge-eating disorder samples than fluoxetine alone (≈5.1 kg vs. ≈2.1 kg). Bupropion monotherapy produced modest but sustained weight loss in some studies (reductions up to 2.4 kg over 52 weeks), while the naltrexone–bupropion combination produced the largest and most reproducible benefits when delivered with structured behavioral modification (9.3% ± 0.4% vs. 5.1% ± 0.6% at 56 weeks). These findings support the use of intensive behavioral therapy alongside targeted pharmacologic antidepressants such as bupropion and naltrexone–bupropion to produce clinically meaningful weight loss in selected settings; however, findings for fluoxetine appear context-dependent. Because trials varied in populations, follow-up duration, and risk-of-bias domains,

these findings should not be interpreted as prescriptive treatment recommendations.

Keywords: Antidepressant therapy; Obesity; Weight loss; Fluoxetine; Cognitive behavioral therapy; Naltrexone–bupropion

1. Introduction

Obesity is a rapidly increasing chronic disease and a global epidemic.¹ According to the World Health Organization (WHO), body mass index (BMI) ≥ 25 kg/m² is considered overweight, and BMI ≥ 30 kg/m² is considered obese.² Additionally, according to the WHO, more than 1.9 billion adults aged 18 years and older are affected by overweight or obesity worldwide.³

In the United States, recent National Health and Nutrition Examination Survey data indicate that approximately 40.3% of adults (over 100 million people) meet the criteria for obesity in the most recent reporting window.⁴ Global estimates for 2021 reported approximately 172 million adults aged ≥ 25 years with obesity, and age-standardized obesity prevalence rose sharply between 1990 and 2021 (approximately 124% in men and 100% in women). If current trends continue, projections suggest that approximately an additional 41.4 million adults will be overweight or obese by 2050 (projected total approximately 213 million), with some models predicting that up to two in three adults in several states in the United States could have obesity by mid-century.⁵ Such individuals are at greater risk for numerous comorbid illnesses, including type 2 diabetes, coronary heart disease, hypertension, gallbladder disease, and osteoarthritis, with an overall increased risk of mortality from all causes.⁶

Obesity is a chronic and multifactorial disease involving the accumulation of subcutaneous and visceral fat, which contributes to the development of many cardiometabolic diseases.^{7,8} The WHO also reports that excessive weight causes the death of almost 3 million people and contributes to disability in 35.8 million people annually.⁸

These systemic processes also interact with central nervous system pathways that regulate appetite, energy balance, and mood. Obesity is associated with hypothalamic inflammation, leptin, and insulin resistance.⁹ Conversely, individuals with obesity commonly report cognitive impairment, anhedonia, and depressive symptoms, which reduce motivation for lifestyle change and worsen quality of life. Because antidepressants act on the brain's monoamine systems that mediate mood, reward, and motivation, their metabolic effects likely reflect both peripheral and central mechanisms, as well as behavioral changes in eating and activity.¹⁰

Behavioral changes in eating habits are evident, as weight change is a common side effect of many antidepressants. Weight changes vary significantly by antidepressant class. Different antidepressant classes affect appetite, satiety, metabolism, and adipose tissue through distinct receptor and neurotransmitter actions, producing either weight gain (via increased intake or altered metabolism) or weight loss or neutral effects (via appetite suppression, increased satiety, or thermogenesis). Data collected from long-term users of antidepressants demonstrate that 65.3% of patients experienced weight gain as an adverse effect, which is relevant given that obesity is 2–3 times more common in individuals with mental illness compared with the general population.^{11,12}

Tricyclic antidepressants, monoamine oxidase inhibitors, and a tetracyclic antidepressant, mirtazapine, are associated with the most substantial weight increases, while selective serotonin reuptake inhibitors (SSRIs) often produce modest short-term weight loss but may be associated with weight gain during longer-term treatment.¹³ Acute increases in synaptic serotonin may suppress appetite and reduce caloric intake, producing transient weight loss; however, adaptive neurobiological and behavioral processes over time can reverse or outweigh these early effects.^{14,15}

Chronic SSRI treatment induces receptor and circuit adaptations in central appetite pathways, notably the downregulation of 5-hydroxytryptamine receptor 2C (5-HT_{2C}) signaling in pro-opiomelanocortin (POMC) neurons, which diminishes anorexigenic melanocortin output and satiety signaling. Experimental work demonstrates that 5-HT_{2C} activity in POMC neurons is sufficient to mediate serotonin's anorectic effects; thus, sustained attenuation of this pathway may shift energy balance toward increased intake.^{16,17} Preclinical animal studies support time-dependent effects. In one paradigm, rats treated with fluoxetine or imipramine under stress for seven days, followed by exposure to a high-fat diet, exhibited increased caloric intake and greater body weight gain approximately 17–22 weeks after drug discontinuation compared with controls ($p < 0.01$).^{14,15}

Tricyclic antidepressant-related weight gain appears to be mediated by several complementary pharmacologic actions. Tricyclic antidepressants commonly antagonize

histamine H1 receptors and muscarinic receptors, leading to increased appetite, sedation, and reduced energy expenditure.¹⁸ Receptor-affinity analyses and meta-analytic reviews indicate that H1 antagonism is a strong predictor of psychotropic-induced weight gain, with additional contributions from 5-HT_{2C} and muscarinic blockade reported across studies.^{14,19,20}

Naltrexone is a μ -opioid receptor antagonist commonly used for the treatment of opioid addiction and alcohol dependence.²¹ Naltrexone reduces food consumption through blockade of β -endorphin signaling at μ -opioid receptors and by preventing autoinhibition feedback on POMC neurons.^{8,22}

Bupropion, a norepinephrine–dopamine reuptake inhibitor, is commonly associated with weight neutrality or modest weight loss in clinical studies, and its pharmacologic stimulation of POMC activity may contribute to this effect.^{23,24} Bupropion promotes weight loss partly via β -endorphin–mediated feedback on POMC neurons. Thus, the efficacy of bupropion and naltrexone together in the treatment of alcohol addiction and smoking cessation may potentially enhance an individual's capacity to regulate their eating behaviors and mitigate food cravings to some extent, leading to gradual weight loss over a period of time.^{25,26}

Antidepressant agents that enhance dopaminergic and noradrenergic tone (e.g., bupropion and naltrexone) often suppress appetite or increase energy expenditure in many patients.²⁷ For example, in a four-day study of 17 obese men, naltrexone reduced food intake by approximately 30% ($p < 0.05$), with approximately 70% of those without adverse symptoms showing appetite suppression.²⁸ Similarly, in a

48-week trial (24-week primary phase) of bupropion SR at 400 mg/day, 83% of participants who completed the study lost $\geq 5\%$ of baseline weight versus 46% in placebo ($p < 0.0001$), indicating reduced energy intake or weight reduction effects in a majority of treated subjects.²⁹ These pharmacodynamic differences help explain the heterogeneity of effects observed in trials.¹⁹

Behavioral therapy—such as cognitive behavioral therapy (CBT)—is the recommended first-line intervention for adults with obesity due to its non-invasive nature and ability to produce clinically meaningful short-term weight loss (typically around 5% of body weight with structured programs).³⁰ However, long-term maintenance is challenging because substantial weight regain is common, with many patients regaining a large portion of lost weight within 1–5 years, and standard behavioral approaches alone often fail to produce durable, large-magnitude weight reductions for individuals with severe obesity.³¹

Consequently, guidelines endorse intensive behavioral therapy as first-line treatment but also recommend pharmacotherapy when greater weight loss is clinically indicated. Given the demonstrated overlap between mood and reward circuits and appetite regulation, evidence that certain antidepressants and drug combinations (e.g., bupropion and naltrexone–bupropion [NB]) can reduce craving and modify appetite suggests that combining psychotherapy with pharmacologic agents may represent a plausible strategy to enhance both short- and long-term weight outcomes. Table 1 presents an overview of different antidepressant classes and their respective roles.

This review aims to synthesize the evidence on the effect of antidepressant therapy on weight-related outcomes such as BMI, body weight, and metabolic markers in adults.

Table 1. Mechanisms of action of selected Food and Drug Administration-approved antidepressants

Antidepressant	Mechanism of action
Tricyclic antidepressant	Cause peripheral metabolic effects that may alter adipose tissue development and reduce lipid utilization; may also induce hypoglycemia, which can stimulate appetite
Monoamine oxidase inhibitor	Block histamine H1 receptors and exert anticholinergic effects, which may reduce satiety and increase carbohydrate craving
Noradrenaline–dopamine reuptake inhibitor	Modulate dopamine and norepinephrine signaling; enhanced dopaminergic neurotransmission may activate hypothalamic melanocortin pathways and suppress appetite (e.g., bupropion)
Selective serotonin uptake inhibitor and multimodal antidepressants (serotonergic agents)	Increase serotonergic activity, which may enhance satiety and reduce food intake; however, long-term use (>1 year) may downregulate 5-HT _{2C} receptors and promote weight gain
Serotonin–norepinephrine reuptake inhibitor	Increase norepinephrine signaling; activation of β_3 -adrenoceptors may enhance thermogenesis (conversion of fat to heat/energy)

Notes: This table summarizes major antidepressant classes and their commonly reported metabolic and appetite-related effects in clinical and preclinical literature. The listed mechanisms are general and not exhaustive; individual agents within each class may differ substantially in their metabolic profiles. Adapted from Gill *et al.*³²

2. Methodology

2.1. Data sources and search strategy

This systematic review was conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.³³ A comprehensive search was performed in PubMed, MEDLINE, Cochrane Library, Web of Science, PsycINFO, Scopus, and Embase databases. The search strategy used the following terms: (antidepress* AND obese) OR (antidepress* AND obesity) OR (antidepress* AND overweight) OR (anti-depress* AND obese) OR (anti-depress* AND obesity) OR (anti-depress* AND overweight). All databases were searched from January 1986 to 2021.

Retrieved studies were screened independently by three reviewers (GA, AR, and ML) using the Covidence platform (Veritas Health Innovation, Australia). Following the removal of duplicates, articles were screened based on title and abstract. Articles were included if deemed relevant by at least two reviewers. Subsequently, full-text articles were assessed against the eligibility criteria. Any discrepancies were resolved through discussion among all reviewers.

During title, abstract, and full-text screening, predefined inclusion and exclusion criteria were applied. Studies were eligible for full-text review only if they met all inclusion criteria and did not meet any exclusion criteria.

Studies were included if they were:

- (i) Randomized controlled trials (RCTs) or prospective controlled clinical trials.
- (ii) Reported a Food and Drug Administration-approved antidepressant agent and assessed obesity-related measures as a primary outcome, secondary outcome, or safety outcome.

Studies were excluded if they were:

- (i) Not written in English.
- (ii) Not peer-reviewed.
- (iii) Lacking full-text availability.

2.2. Data extraction and quality assessment

From the included studies, data extraction was conducted independently by three reviewers (GA, AR, and ML) using a piloted data extraction form in Microsoft Excel 2021 MSO (Microsoft Corporation, United States) (Table 2). The data extraction variables were predefined, and any discrepancies were resolved through discussion among all authors. Extracted data included: (i) study design, (ii) intervention used, (iii) sample size, (iv) participant age, (v) biomarker(s) of interest, (vi) measurement tool(s), and (vii) primary outcome(s).

To assess methodological quality and potential risk of bias (RoB) in the included studies, RoB assessment tools were selected according to study design. The Cochrane

Table 2. Study demographics and outcomes

No.	Study	Intervention	Sample size (n)	Sample age (years)	Study duration	Measurement tools	Outcomes
1	Macias-Cortes <i>et al.</i> ³⁴	(i) Fluoxetine (20 mg/day) (ii) IHT	133	~49	6 weeks	HRSD, metabolic markers (e.g., BMI, triglycerides, cholesterol, HOMA-IR, TSH)	Combined IHT and fluoxetine produced >50% reduction in depressive symptoms, as measured by HRSD
2	Mansoor <i>et al.</i> ³⁵	(i) SSRIs (e.g., paroxetine, citalopram, fluoxetine) (ii) Venlafaxine (iii) CBT	296	~15.8	24 weeks	(i) CDRS-R (ii) BDI (iii) SIQ-Jr (iv) SCARED (v) GI-S/I (vi) BMI z-scores	In adolescents with treatment-resistant depression, baseline BMI and treatment outcomes were bidirectionally associated: baseline BMI predicted likelihood of remission, and remission (A-LIFE = 1 for ≥3 weeks) was associated with subsequent changes in BMI z-score

(Cont'd...)

Table 2. (Continued)

No.	Study	Intervention	Sample size (n)	Sample age (years)	Study duration	Measurement tools	Outcomes
3	McIntyre <i>et al.</i> ³⁶	Extended-release NB (32/360 mg) vs. placebo	8,894	~61	104 weeks	Body weight, BMI, waist circumference, percentage weight change, adverse effect incidence	NB increased the likelihood of achieving clinically meaningful weight loss ($\geq 5\%$, $\geq 10\%$, $\geq 15\%$) compared with placebo plus lifestyle intervention in patients with overweight or obesity. Efficacy was observed across subgroups stratified by baseline antidepressant use, indicating benefit irrespective of concomitant antidepressant therapy
4	Devlin <i>et al.</i> ³⁷	(i) Fluoxetine (ii) Placebo (iii) CBT + fluoxetine (iv) CBT + placebo Dosing: The initial dosage was 20 mg/day, titrated to 60 mg/day after 4–5 weeks	116	43 $\pm$ 12	20 weeks	(i) BSQ (ii) BES (iii) BSI (iv) RSE (v) TFEQ (vi) IIP (vii) scq-BED (viii) SCID (ix) BMI	In a trial evaluating CBT and fluoxetine as adjuncts to group behavioral therapy for binge-eating disorder, participants receiving individual CBT showed significantly greater reductions in binge-eating frequency than those not receiving CBT
5	Abell <i>et al.</i> ³⁸	Fluvoxamine maleate (50 mg) was administered orally twice daily	29	18–60	12 weeks	(i) BDI (ii) Foulds and Bedford Social Anxiety–Depression Scale (iii) Fluvoxamine plasma levels (iv) BMI	Fluvoxamine produced a modestly greater reduction in body weight than placebo (3.5 kg vs. 2.8 kg), while mood improved in both groups. However, the small absolute difference limits conclusions regarding clinical superiority for metabolic outcomes; larger and longer-duration trials are required to confirm a treatment-related effect on weight
6	Croft <i>et al.</i> ³⁹	Bupropion-SR was administered orally at 150 mg once daily for the first 3 days, followed by 150 mg twice daily during the 8-week open-label phase	423	18–74	52 weeks	(i) CGI-I (ii) 21-item HRSD	Bupropion-SR was associated with modest but sustained weight loss (up to –2.4 kg) over 52 weeks, with greater effects observed in participants with higher baseline BMI. These findings suggest that bupropion may provide a clinically meaningful weight-reducing benefit in some patients with major depressive disorder
7	Bondi <i>et al.</i> ⁴⁰	Fluoxetine was administered orally	32	45–55	12 weeks	(i) REE (ii) OGTT (iii) Beck Depression Inventory for Screening	In obese menopausal women, acute fluoxetine administration resulted in a small increase in REE; however, no significant effects were observed on insulin, respiratory quotient, or glucose-induced thermogenesis

(Cont'd...)

Table 2. (Continued)

No.	Study	Intervention	Sample size (n)	Sample age (years)	Study duration	Measurement tools	Outcomes
8	Dastjerdi <i>et al.</i> ⁴¹	Fluoxetine (20 mg/day) was administered orally in combination with metformin (500 mg three times daily) alongside dietary and behavioral therapy	91	~31.67	6–80 weeks	(i) BMI (ii) Interview and pill count (iii) Medical scale and questionnaire	Combined fluoxetine and metformin produced substantial weight loss (–7.89 kg, –9.32% BMI) compared with minimal changes in controls (–0.48 kg, –0.42% BMI), with greater effects observed beyond 6–12 months of treatment. No serious side effects were reported
9	Jha <i>et al.</i> ⁴²	(i) Escitalopram + placebo (ii) Bupropion-SR + escitalopram (iii) Venlafaxine-XR + mirtazapine	665	18–75	12 weeks	(i) QIDS-SR16 (ii) BMI at baseline	Baseline BMI did not significantly moderate overall antidepressant treatment outcomes. A non-significant trend toward lower response was observed in the higher-BMI subgroup receiving venlafaxine plus mirtazapine; however, this did not reach statistical significance, indicating that BMI alone is not a robust predictor of antidepressant efficacy in this dataset
10	Molinari <i>et al.</i> ⁴³	(i) Fluoxetine (ii) CBT	34	~37	18 weeks	(i) EDE-Q (ii) BDI	Across interventions for binge-eating disorder in obesity, all treatments reduced binge episodes and depressive symptoms; however, combined pharmacologic-behavioral therapy produced the greatest weight loss (≈5.1 kg), compared with fluoxetine alone (≈2.1 kg) or CBT alone (≈3.4 kg)
11	Rubin <i>et al.</i> ⁴⁴	(i) ILI (ii) Diabetes support and education	5,145	~59	4 years	(i) BDI (ii) Antidepressant medication records (iii) BMI	Participants randomized to ILI achieved greater weight loss without a significant increase in antidepressant use, supporting the efficacy of structured lifestyle programs for metabolic improvement
12	Grilo <i>et al.</i> ⁴⁵	CBT combined with fluoxetine or placebo; fluoxetine (or placebo) was administered at 60 mg/day. CBT was delivered as weekly individual 60-minute sessions for four months	81	18–60	16 weeks	(i) SPSS (ii) OBEs (iii) EDE-Q (iv) GEE	At 12-month follow-up, CBT-containing interventions outperformed fluoxetine monotherapy: remission rates were 3.7% for fluoxetine alone, 26.9% for CBT + fluoxetine, and 35.7% for CBT + placebo. Overall, CBT produced substantially greater and more durable clinical benefit than fluoxetine alone, with no meaningful difference between CBT + fluoxetine and CBT + placebo

(Cont'd...)

Table 2. (Continued)

No.	Study	Intervention	Sample size (<i>n</i>)	Sample age (years)	Study duration	Measurement tools	Outcomes
13	Green <i>et al.</i> ⁴⁶	Escitalopram, sertraline, or venlafaxine-XR were administered for 8 weeks. Dosage was expressed in mg/day for sertraline and venlafaxine-XR. For escitalopram, the dosage (mg/day) was multiplied by a factor of 10 to align its distribution with the other treatment dosages for group-level analyses	659	18–65	8 weeks	(i) SPSS (ii) HRSD (iii) BMI	Higher baseline BMI predicted greater remission with venlafaxine-XR, particularly for physical symptoms ($b = 0.15$, $p = 0.003$). No significant sex differences were observed in mean changes for cognitive symptoms ($F[1,656] = 0.26$, $p = 0.61$) or physical/vegetative symptoms ($F[1,655] = 1.32$, $p = 0.25$). However, in females, higher BMI was associated with greater improvement in cognitive symptoms across treatments ($b = 0.13$, $p = 0.011$), suggesting BMI-related heterogeneity in treatment response that may inform personalized antidepressant selection
14	Wadden <i>et al.</i> ⁴⁷	NB32 was administered as an adjunct to intensive behavioral modification	793	18–65	56 weeks	Body weight	NB32, combined with behavioral modification, produced significantly greater weight loss than placebo plus behavioral modification at 56 weeks ($9.3\% \pm 0.4\%$ vs. $5.1\% \pm 0.6\%$; $p < 0.001$). Results were consistent across analyses, including completers ($11.5\% \pm 0.6\%$ vs. $7.3\% \pm 0.9\%$; $p < 0.001$) and intent-to-treat populations ($7.8\% \pm 0.4\%$ vs. $4.9\% \pm 0.6\%$; $p < 0.001$). A significantly higher proportion of participants receiving NB32 achieved $\geq 5\%$ and $\geq 10\%$ weight loss, along with greater improvements in cardiometabolic risk markers
15	Hazuda <i>et al.</i> ⁴⁸	Antidepressant medications, including SSRI, SNRI, and TCA	5,145	45–76	9.6 years	BDI-1A, cardiovascular event adjudication (e.g., CVD death, nonfatal MI, stroke, angina)	Depressive symptoms and antidepressant use were associated with sex-specific differences in incident CVD: in men, a BDI score ≥ 10 combined with antidepressant use was associated with increased CVD risk, whereas in women antidepressant use was associated with reduced CVD risk
16	Hollander <i>et al.</i> ⁴⁹	Naltrexone-SR 32 mg/day administered in combination with bupropion-SR (360 mg/day) vs. placebo	505	18–70	56 weeks	(i) Body weight (ii) HbA1c (iii) Waist circumference (iv) IDS-SR	No significant differences were observed in weight, metabolic, or inflammatory outcomes between antidepressant users and non-users

(Cont'd...)

Table 2. (Continued)

No.	Study	Intervention	Sample size (n)	Sample age (years)	Study duration	Measurement tools	Outcomes
17	Imayama <i>et al.</i> ⁵⁰	Dietary intervention targeting 10% weight loss, combined with exercise (225 min/week of moderate-to-vigorous aerobic activity)	439	50–75	52 weeks	(i) Body weight (ii) Waist circumference (iii) Percentage body fat (iv) Glucose level (v) Insulin level (vi) HOMA-IR (vii) hs-CRP	No significant differences in weight, metabolic, or inflammatory outcomes were observed between antidepressant users and non-users following diet and exercise interventions
18	Gunnarsdóttir <i>et al.</i> ⁵¹	Four isocaloric energy-restricted diets providing a 30% reduction in energy intake from estimated energy expenditure	114	20–40	8 weeks	(i) Body weight (ii) Waist circumference (iii) BMI (iv) Soft drink consumption	Antidepressant use was significantly higher among trial dropouts than completers (19.2% vs. 1.8%, $p < 0.001$), and dropouts consumed 35% more soft drinks ($p = 0.012$), with borderline age differences. These findings suggest that antidepressant use and high sugary beverage intake may be predictors of attrition in weight-loss trials
19	Toups <i>et al.</i> ⁵²	(i) Escitalopram + placebo (ii) Bupropion + escitalopram (iii) Venlafaxine + mirtazapine	662	18–75	28 weeks	(i) BMI (ii) HRSD (iii) PDSQ (iv) SCQ (v) QIDS	Remission rates did not differ across BMI categories; however, lower BMI was associated with a higher frequency of adverse effects. These findings suggest that BMI does not predict antidepressant remission but may influence tolerability

Notes: This table presents a summary of included studies, including intervention arms, sample sizes (n), participant age, study duration, measurement instruments, and primary outcomes as reported in the original publications. The total pooled sample comprised 24,256 participants, with study sample sizes ranging from 32 to 5,145 participants. Study duration ranged from 6 weeks to 9.6 years, and these included studies were randomized controlled trials. Values are reported as presented in the source articles.

Abbreviations: BDI: Beck Depression Inventory; BES: Binge Eating Scale; BMI: Body mass index; BSQ: Body Shape Questionnaire; BSI: Brief Symptom Inventory; CBT: Cognitive behavioral therapy; CDRS-R: Children's Depression Rating Scale–Revised; CGI-I: Clinical Global Impression–Improvement; CVD: Cardiovascular disease; EDE-BED: Eating Disorder Examination–Binge Eating Disorder module; EDE-Q: Eating Disorder Examination Questionnaire; GEE: General estimating equations; GI-S/I: Gastrointestinal Symptom–Severity/Impact; hs-CRP: High-sensitivity C-reactive protein; HRSD: Hamilton Rating Scale for Depression; IHT: Individualized homeopathic treatment; IIP: Inventory of Interpersonal Problems; IDS-SR: Inventory of Depressive Symptomatology–Self Report; ILI: Intensive lifestyle intervention; MI: Myocardial infarction; NB: Naltrexone–bupropion; OGTT: Oral glucose tolerance test; OBE: Objective binge eating episodes; PDSQ: Psychiatric Diagnostic Screening Questionnaire; QIDS: Quick Inventory of Depressive Symptomatology; QIDS-SR16: Quick Inventory of Depressive Symptomatology–Self Report 16-item; REE: Resting energy expenditure; RSE: Rosenberg Self-Esteem Scale; SCARED: Screen for Child Anxiety Related Emotional Disorders; SCID: Structured Clinical Interview for DSM Disorders; SCQ: Self-Administered Comorbidity Questionnaire; SIQ-Jr: Suicidal Ideation Questionnaire–Junior; SNRI: Serotonin–norepinephrine reuptake inhibitor; SR: Sustained release; SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic antidepressant; TFEQ: Three-Factor Eating Questionnaire; TSH: Thyroid-stimulating hormone; XR: Extended release.

RoB 2.0 (Cochrane Bias Methods Group, United Kingdom) tool⁵³ was used to assess RCTs, evaluating five domains: (i) random sequence generation and allocation concealment, (ii) blinding of participants and personnel, (iii) blinding of outcome assessment, (iv) complete outcome data, and (v) selective reporting.⁵⁴

In this review, the WHO BMI thresholds were applied

(overweight: BMI ≥ 25 kg/m²; obesity: BMI ≥ 30 kg/m²). However, because included studies reported heterogeneous obesity-related outcomes, a study was considered eligible if it reported any clinically relevant measure of adiposity or metabolic risk, including BMI or BMI z-score, body weight (kg), percentage weight change from baseline, waist circumference, body fat percentage, or metabolic markers.

3. Results

3.1. Study characteristics of included studies

The search yielded 222 records. Of the 156 screened citations, 37 full-text articles were assessed for eligibility. (Figure 1) A total of 18 studies were excluded at full-text review: 11 lacked full-text availability, and 7 did not report any prespecified obesity-related outcomes (e.g., body weight, BMI/BMI z-score, percentage weight change, waist circumference, body fat percentage, or metabolic markers). The final selection comprised 19 eligible studies, which fulfilled the predefined inclusion criteria (Section 2.1). Most included studies involved adult populations, while only one study focused on adolescents (mean age = 15.8 years). In total, the included studies comprised data from 24,256 participants, with sample sizes ranging from 32 to 5,145 study participants. The Cochrane RoB 2.0 tool was used to assess the methodological quality of the 19 RCTs (Table 3).

Risk of bias was assessed using the Cochrane RoB 2.0 tool. Domain-level judgments are presented in the table for each RCT. Domain definitions (as specified in RoB 2.0)⁵³ are as follows:

- (i) Bias arising from the randomization process includes concerns about sequence generation and allocation concealment.
- (ii) Bias due to deviations from intended interventions includes issues related to adherence, co-interventions, or the analysis population.
- (iii) Bias due to missing outcome data includes incomplete outcome reporting or differential attrition.
- (iv) Bias in the measurement of the outcome includes concerns regarding blinding of outcome assessors or measurement validity.
- (v) Bias in the selection of the reported result refers to selective outcome reporting or outcome switching.

Overall, the included RCTs demonstrated acceptable methodological quality, with most studies being classified as low risk across key domains. However, several studies exhibited moderate risk, principally related to deviations from intended interventions, selective reporting, or missing outcome data. For example, Grilo *et al.*⁴⁵ reported substantial attrition, with approximately 28% of randomized participants not completing 12-month follow-up assessments (Table 3). Taken together, these findings suggest that the randomized evidence is generally reliable; however, results should be interpreted cautiously in light of study limitations.

3.2. Fluoxetine and other selective serotonin reuptake inhibitors

Across multiple studies, fluoxetine demonstrated variable

but generally favorable effects on weight and metabolic outcomes. In one RCT comparing individualized homeopathic treatment, fluoxetine (20 mg/day), and placebo, fluoxetine achieved significant depression response rates ($\geq 50\%$ reduction in Hamilton Rating Scale for Depression), although associations with metabolic markers such as BMI, triglycerides, cholesterol, homeostatic model assessment for insulin resistance, and thyroid-stimulating hormone were inconsistent.³⁴

In the HOMDEP-MENOP randomized trial involving Mexican peri- and post-menopausal women, metabolic dysregulation was highly prevalent at baseline (86.5% overweight/obesity, 52.3% hypertriglyceridemia, 46.7% insulin resistance, and 16% subclinical hypothyroidism). However, none of the metabolic parameters were significantly associated with nonresponse to fluoxetine or to the homeopathic intervention in bivariate analysis (e.g., for hypertriglyceridemia: odds ratio [OR] = 1.57, 95% confidence interval = 0.46–5.32, $p = 0.467$; for insulin resistance: OR = 0.67, 95% confidence interval = 0.16–2.70, $p = 0.579$).

In eating disorder trials, fluoxetine combined with CBT produced greater reductions in binge episodes and depressive symptoms than fluoxetine alone, with a mean weight loss of approximately 5.1 kg compared with 2.1 kg for the fluoxetine-only group and 3.4 kg for the CBT-only group. Remission rates differed significantly across groups; at 12 months, rates were 3.7% for fluoxetine-only and 26.9% for CBT + fluoxetine, as assessed using various eating disorder measures, including objective binge episodes and the Eating Disorder Examination Questionnaire, with statistical analyses performed using general estimating equations, indicating stronger efficacy of psychotherapy combined with pharmacotherapy compared with pharmacotherapy alone.⁴⁵

Another trial of oral fluoxetine combined with metformin reported significant weight reduction (−7.89 kg and −9.32% BMI) compared with minimal change in controls (−0.48 kg and −0.42% BMI; $p < 0.05$). Acute fluoxetine increased resting energy expenditure, while chronic administration was associated with maintenance of resting energy expenditure, lower fasting glucose, and non-significant weight loss without effects on insulin or thermogenesis markers.⁴⁰

Among other SSRIs, fluvoxamine (50 mg twice daily) produced slightly greater weight loss than placebo (−3.5 kg vs. −2.8 kg), alongside mood improvements in both groups. Escitalopram and sertraline showed limited effects on weight; however, in an eight-week trial, higher BMI predicted greater remission with venlafaxine XR ($b = 0.15$, $p = 0.003$), with additional findings in females showing that

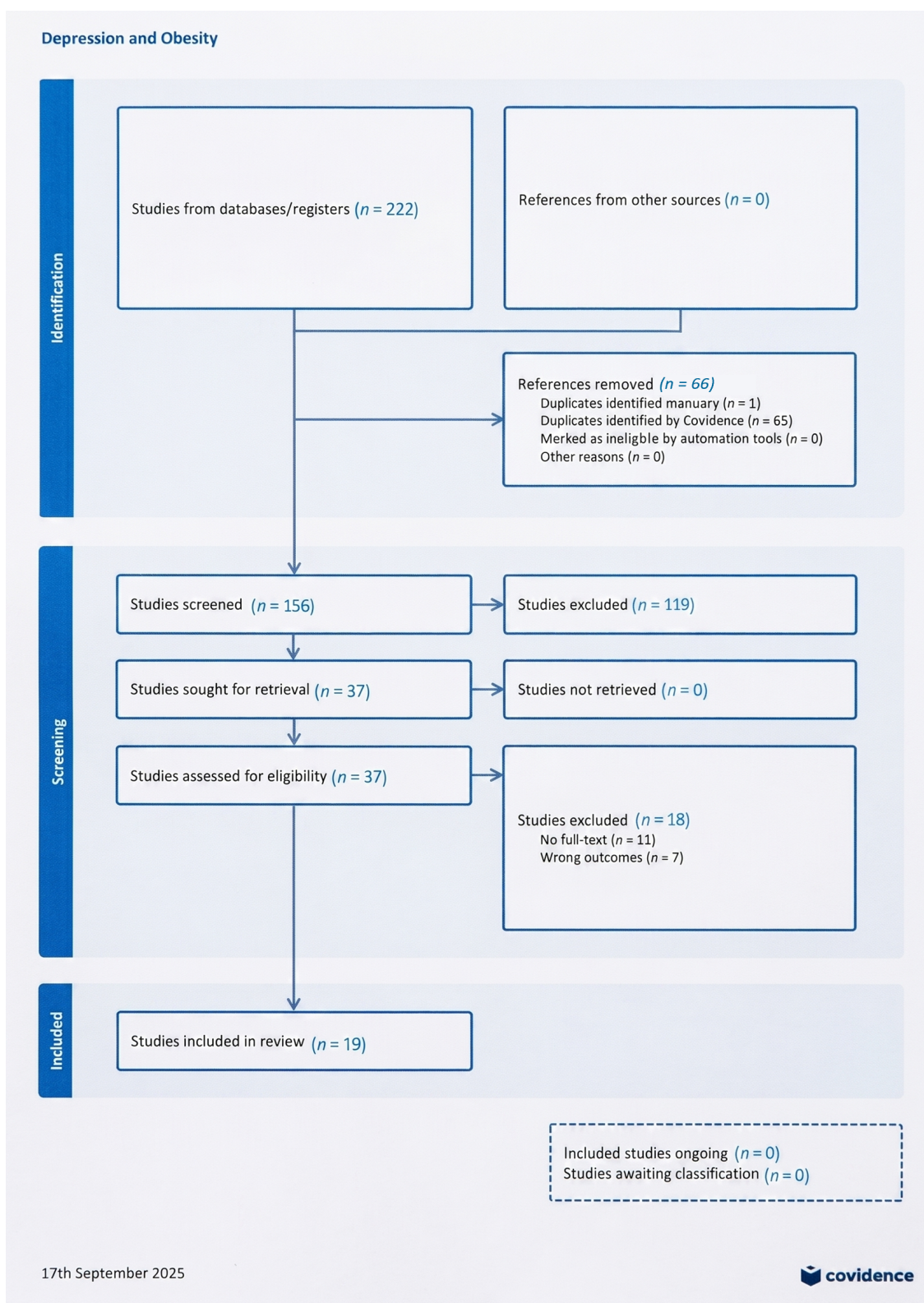


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram

Table 3. Summary of study quality and bias assessment in randomized trials

No.	Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in the measurement of the outcome	Bias in the selection of the reported result
1	Macias-Cortes <i>et al.</i> ³⁴	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
2	Mansoor <i>et al.</i> ³⁵	Low risk	Moderate risk	Moderate risk	Low risk	Moderate risk
3	McIntyre <i>et al.</i> ³⁶	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
4	Devlin <i>et al.</i> ³⁷	Low risk	Low risk	Low risk	Low risk	Low risk
5	Abell <i>et al.</i> ³⁸	Low risk	Moderate risk	Moderate risk	Low risk	Low risk
6	Croft <i>et al.</i> ³⁹	Low risk	Low risk	Moderate risk	Low risk	Low risk
7	Bondi <i>et al.</i> ⁴⁰	Moderate risk	Low risk	Low risk	Low risk	Low risk
8	Dastjerdi <i>et al.</i> ⁴¹	High risk	High risk	Moderate risk	Moderate risk	Low risk
9	Grilo <i>et al.</i> ⁴⁵	Low risk	Low risk	Moderate risk (28% did not complete the trial)	Low risk	Low risk
10	Green <i>et al.</i> ⁴⁶	Low risk	Low risk	Low risk	Low risk	Moderate risk (secondary analysis)
11	Wadden <i>et al.</i> ⁴⁷	Low risk	Low risk	Low risk	Low risk	Low risk
12	Hazuda <i>et al.</i> ⁴⁸	Low risk	Low risk	Low risk	Low risk	Low risk
13	Hollander <i>et al.</i> ⁴⁹	Low risk	Low risk	Low risk	Low risk	Low risk
14	Imayama <i>et al.</i> ⁵⁰	Low risk	Low risk	Low risk	Low risk	Low risk
15	Gunnarsdóttir <i>et al.</i> ⁵¹	Low risk	Low risk	Moderate risk	Low risk	Moderate risk
16	Toups <i>et al.</i> ⁵²	Low risk	Moderate risk	Low risk	Low risk	Low risk

Notes: Of the 19 randomized controlled trials included in the review, 16 were assessed using the Cochrane RoB 2.0 tool. Three studies were excluded from risk-of-bias assessment due to insufficient information required for full evaluation.

higher BMI predicted cognitive symptom improvement ($b = 0.13$, $p = 0.011$).⁴⁶

3.3. Bupropion and naltrexone–bupropion combination

Bupropion monotherapy was consistently associated with modest weight loss. In a single study, bupropion SR led to weight reductions of up to 2.4 kg, which were sustained over 52 weeks, particularly among participants with higher baseline BMI.³⁹

Combination therapy with NB demonstrated more pronounced weight reduction outcomes. At week 56, NB with behavioral modification achieved a mean weight loss of 9.3% versus 5.1% for placebo ($p < 0.001$). Participants who completed the study lost $11.5 \pm 0.6\%$ compared with $7.3 \pm 0.9\%$ in placebo ($p < 0.001$), and intent-to-treat analyses confirmed the superiority of NB ($7.8 \pm 0.4\%$ vs. $4.9 \pm 0.6\%$; $p < 0.001$). Significantly more participants in the NB group achieved $\geq 5\%$ and $\geq 10\%$ weight loss. NB treatment also improved HbA1c, fasting glucose, and waist circumference compared with placebo, although nausea and constipation were reported more frequently as adverse events.⁴⁷

When stratified by baseline antidepressant use, NB maintained efficacy in achieving $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ weight loss across subgroups, without significant worsening of depressive symptoms, as assessed by the Montgomery–Åsberg Depression Rating Scale and Clinical Global Impression–Improvement scale.³⁶

3.4. Venlafaxine and mirtazapine combinations

Venlafaxine–mirtazapine combinations produced mixed outcomes. In one study, remission rates were similar across combinations such as escitalopram + placebo (38.8%), bupropion + escitalopram (38.9%), and venlafaxine + mirtazapine (37.7%); however, the venlafaxine–mirtazapine combination showed a higher side-effect burden (mean number of worsening adverse events was 5.7 vs 4.7 for escitalopram + placebo). Commonly reported mirtazapine-related adverse effects contributing to this increased burden include somnolence, increased appetite/weight gain, dry mouth, and dizziness.^{42,46,55}

3.5. Escitalopram and multi-agent comparisons

Trials combining escitalopram with placebo, bupropion SR, or venlafaxine–mirtazapine showed no significant differences in depression remission between BMI classes. Secondary analyses revealed BMI-related differences in tolerability, with participants with lower BMI reporting more adverse effects. Commonly reported problems with the venlafaxine–mirtazapine combination included

somnolence/daytime sedation, increased appetite, dry mouth, dizziness, and gastrointestinal complaints.^{42,46,52}

4. Discussion

This review synthesizes evidence on the effects of antidepressant treatments on obesity-related outcomes. Of 222 records identified, 19 eligible studies comprising 24,256 participants were included. Across these trials, bupropion monotherapy produced modest, sustained weight reductions of up to 2.4 kg over 52 weeks in a single trial.³⁹ Fluoxetine showed variable but generally favorable weight-related effects that were consistently larger when combined with structured psychotherapy (fluoxetine + CBT resulted in approximately 5.1 kg mean weight loss vs. 2.1 kg for fluoxetine alone and 3.4 kg for CBT alone in eating-disorder-related trials; remission at 12 months was 3.7% for fluoxetine-only vs. 26.9% for CBT + fluoxetine vs. 35.7% for CBT + placebo). Lastly, NB combination therapy yielded the largest and most reproducible effects (NB + behavior modification [BMOD] produced 9.3% mean weight loss vs. 5.1% for placebo + BMOD at 56 weeks; completers: $11.5 \pm 0.6\%$ vs $7.3 \pm 0.9\%$; intent-to-treat: $7.8 \pm 0.4\%$ vs. $4.9 \pm 0.6\%$; all $p < 0.001$).^{36,47}

The superiority of combined treatment (e.g., fluoxetine + CBT) reflects complementary and potentially mutually reinforcing mechanisms rather than a single pharmacological effect.⁵⁶ Pharmacotherapy may reduce biological and affective barriers to behavioral change, including reducing appetite, craving, and anhedonia, thereby improving patients' capacity to engage with and apply therapeutic skills. At the same time, antidepressant-related modulation of neural plasticity and synaptic remodeling may facilitate a transient learning window, during which CBT techniques—such as self-monitoring, cognitive restructuring, and relapse prevention—may be more effectively acquired and consolidated.

Evidence from rapid-acting agents (e.g., ketamine) suggests that pharmacologic enhancement of plasticity can increase the effectiveness of subsequent psychotherapeutic learning, providing a mechanistic rationale for combining agents that promote neural flexibility with learning-based therapies.⁵⁷ These mechanistic synergies are supported by clinical findings, where combined treatment arms typically yield larger short-term weight loss and improved longer-term clinical outcomes. For example, eating disorder trials reported mean weight loss of approximately 5.1 kg for fluoxetine + CBT versus approximately 2.1 kg for fluoxetine alone, alongside substantially higher 12-month remission rates for combined therapy. This suggests that pharmacotherapy-assisted facilitation of learning and behavioral consolidation may contribute to greater and more durable benefits than either approach alone.⁵⁸

The observed efficacy gradient aligns with known pharmacology. Tricyclics and mirtazapine, both strong H1 antagonists and, in some cases, 5-HT_{2C} antagonists, are consistently associated with weight gain via increased appetite, sedation, and reduced energy expenditure.¹⁹ SSRIs (e.g., fluoxetine) commonly produce transient anorectic effects; however, preclinical findings suggest that chronic SSRI exposure can induce receptor and circuit adaptations (e.g., downregulation of 5-HT_{2C} receptors on POMC neurons and a relative shift toward NPY/AgRP signaling), which may attenuate early weight benefits, particularly in obesogenic environments (animal models showed delayed weight increases after short SSRI exposure; $p < 0.01$).⁵⁹

Bupropion (a norepinephrine–dopamine reuptake inhibitor) exerts noradrenergic and dopaminergic effects that may increase POMC activity and reduce reward-driven eating in some patients, consistent with the modest but reproducible weight losses observed in trials. NB combines these mechanisms, where bupropion stimulates POMC neurons while naltrexone blocks μ -opioid-mediated autoinhibition of POMC, producing sustained anorexigenic signaling, a mechanism consistent with the largest observed percentage weight losses in NB trials.⁴⁷

4.1. Clinical implications

For clinicians treating patients with overweight, obesity, and comorbid depression, the findings support a pragmatic, individualized approach: bupropion is preferred when weight neutrality or modest loss is desired (trial evidence that 83% of participants who completed the study lost $\geq 5\%$ of baseline weight versus 46% with placebo; $p < 0.0001$);²⁹ fluoxetine combined with CBT may be considered when psychotherapy is available and behavioral drivers (e.g., binge eating) predominate (combined trials show ≈ 5.1 kg mean weight loss and higher remission);⁴³ and NB with structured behavioral modification may be used when larger, sustained weight reductions are indicated, with attention to adverse effects (e.g., higher rates of nausea and constipation) and the need for psychiatric monitoring. Importantly, these approaches should be implemented as adjuncts within a stepped-care model that prioritizes safety and patient preference.⁶⁰

There is growing evidence that antidepressant effects and utilization patterns differ by sex and race, with implications for weight-related outcomes and health equity. Several population and cohort studies report sex-specific associations between antidepressant exposure and weight change; for example, long-term SSRI exposure is associated with modest weight gain in women (+0.74 kg) but not in men ($p = 0.002$).⁶¹ Marked racial and ethnic disparities in antidepressant use persist: United States

surveillance data indicate higher use among non-Hispanic White adults (16.6%) compared with non-Hispanic Black (7.8%), Hispanic (6.5%), and non-Hispanic Asian adults (2.8%). Use also increases with age (7.9% [18–39 years], 14.4% [40–59 years], and 19.0% [≥ 60 years]), and was 13.6% overall among adults in 2015–2018, with higher prevalence in divorced, separated, or widowed adults (20.5%) than in married (12.3%) or unmarried (10.8%) groups; women consistently show higher use than men across strata.⁶²

These differences are likely multifactorial, reflecting variations in help-seeking behavior, provider prescribing patterns, structural barriers, and potentially differences in pharmacologic or metabolic susceptibility.⁶³ Accordingly, future studies should report and stratify outcomes by age, sex, marital status, and race.

In the HOMDEP-MENOP trial, despite high baseline rates of metabolic disorders (e.g., hypertriglyceridemia = 52.3%, insulin resistance = 46.7%), none were significantly associated with treatment nonresponse (e.g., hypertriglyceridemia: OR = 1.57, $p = 0.467$; insulin resistance: OR = 0.67, $p = 0.579$). This finding suggests that metabolic dysregulation was not a strong predictor of antidepressant nonresponse in this cohort. However, wide confidence intervals and p -values approaching significance (e.g., $p = 0.059$ for overweight) suggest potential underpowering or sample heterogeneity; thus, larger and more representative cohorts are needed to clarify these associations.³⁴

4.2. Limitations and future directions

This review has several important limitations. First, the synthesis was restricted to RCTs to maximize internal validity; although this strengthens causal inference, it limits detection of long-term safety signals, rare adverse events, and real-world effectiveness that well-conducted observational studies may capture. Second, some trials had methodological limitations that constrain the strength of the evidence. For example, substantial attrition in Grilo *et al.*⁴⁵ (approximately 28% non-completion at 12 months) and evidence of selective outcome reporting in a subset of studies. Third, outcome definitions and reporting were inconsistent (e.g., body weight in kg, percentage weight change, BMI, waist circumference, and metabolic markers), limiting comparability across trials. Collectively, these limitations highlight the need for larger, longer-duration, and more standardized trials, alongside high-quality observational studies to assess durability and generalizability.

A promising direction for future pharmacologic and psychotherapeutic interventions is to pair mechanistically

complementary treatments with scalable psychotherapies. CBT and structured behavioral modification programs represent practical platforms: CBT demonstrates moderate, clinically meaningful effects on binge eating and weight-related behaviors and can be widely delivered (including via digital formats), whereas intensive BMOD achieves greater weight reduction when delivered with frequent contact and structured counseling.⁶⁴

Future studies should evaluate whether concurrent use of weight-loss pharmacotherapies, such as glucagon-like peptide-1 receptor agonists (e.g., semaglutide), directly reduces depressive symptoms and whether such effects contribute to subsequent weight reduction. This question is particularly relevant given ongoing clinical trials of semaglutide in individuals with obesity and comorbid major depressive disorder, which may clarify the potential of integrated metabolic–psychiatric treatment strategies.

5. Conclusion

Randomized trials indicate that some antidepressant regimens affect body weight in clinically meaningful ways. Bupropion monotherapy produces modest but consistent weight reduction across trials (approximately 2.4 kg over one year), whereas the NB combination yields the largest and most reproducible percentage weight loss. Fluoxetine's effects are context-dependent and appear greatest (approximately 5.1 kg weight loss) in trials combining pharmacotherapy with psychotherapy or adjunctive interventions. Because included trials vary in population characteristics, follow-up duration, and RoB domains, these findings should not be interpreted as prescriptive treatment guidance. Clinical application requires individualized clinical judgment, with careful consideration of efficacy, safety, contraindications, and patient preferences. Future research should integrate long-term and high-quality observational data to better assess durability and rare adverse outcomes.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

This manuscript is a systematic review of previously published studies and does not involve recruitment of new human participants, animals, or primary patient-derived cell lines. Therefore, formal ethical approval and Institutional Review Board review were not required. All data analyzed were obtained from publicly available, published sources.

Consent for publication

Not applicable. No individual participant-level data or identifying images are reported in this review. All information presented is aggregated from published studies.

Availability of data

The results reported in the manuscript are based on data extracted from published articles identified through searches of PubMed, MEDLINE, Cochrane Library, Web of Science, PsycINFO, Scopus, and Embase. Summary tables and the data underpinning the analyses are presented within the manuscript. The full data extraction spreadsheet and the analysis code used for summary statistics are available from the corresponding author upon reasonable request.

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