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Effects of Weight Loss Medications on Cardiometabolic Risk Profiles: A Systematic Review and Network Meta-Analysis

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Abstract

Background & Aims—We performed a systematic review and network meta-analysis to evaluate the overall and comparative effects of weight-loss medications, approved by the Food and Drug Administration (FDA) for long-term use, on cardiometabolic risk profiles of obese adults.

Methods—We performed a systematic literature review through February 28, 2017 to identify randomized clinical trials of the effects of FDA-approved weight loss medications (orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, and liraglutide), administered to obese adults for 1 year or more, compared with placebo or another active agent. Outcomes of interest included changes in blood glucose (fasting blood glucose [FBG] and hemoglobin A1c [A1c]), cholesterol profile (low-density lipoprotein and high-density lipoproteins [HDL]), blood pressure (systolic/diastolic) and waist circumference (WC). We performed pair-wise and network meta-analyses with outcomes reported as weighted and standardized mean differences. Quality of evidence was rated using GRADE.

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Results—In a meta-analysis of 28 randomized controlled trials (29018 participants; median body mass index, 36.1kg/m2), we associated weight-loss medications with a modest decrease in FBG (weighted mean difference, 4.0 mg/dL; 95% CI, −4.4 to −3.6) and WC (weighted mean difference, reduction of 3.3 cm; 95% CI, −3.5 to −3.1), without clinically meaningful changes in systolic/diastolic blood pressure or cholesterol profile vs placebo (standardized mean difference below 0.2); effects varied among drugs. Phentermine-topiramate use was associated with a substantial decrease in WC and a modest decrease in FBG, A1c, and blood pressure and had minimal effect on cholesterol. Liraglutide use was associated with a substantial decrease in FBG, A1c, and WC and a minimal effect on blood pressure and cholesterol. Naltrexone-bupropion use was associated with moderate increase in HDL cholesterol but had a minimal effect on FBG and WC. Orlistat use was associated with a decrease in low-density lipoprotein and HDL-cholesterol. No drug improved all cardiometabolic risk factors.

Conclusions—In a systematic review and network meta-analysis, we found FDA-approved weight loss medications to have only modest positive effects on cardiometabolic risk profile. Further research is needed to evaluate the long-term cardio-metabolic benefits of these medications. PROSPERO: CRD42016039486

Keywords

BMI; heart disease; vascular; pharmacotherapy

INTRODUCTION

Obesity is associated with an unfavorable cardiometabolic risk-factor profile,[1] which portends an excess risk of cardiovascular morbidity and mortality. Lifestyle interventions have only been modestly effective in alleviating this excess risk.[2] Pharmacological therapies for obesity are promising, with varying efficacy for weight loss.[3] The average weight loss with the five agents approved for long-term management of obesity by the U.S. Food and Drug Administration (FDA) – orlistat, lorcaserin, naltrexone-bupropion, liraglutide, and phentermine-topiramate – ranges from 2.6–8.8kg over placebo, with approximately 20–54% patients achieving ≥10% weight loss after a year of therapy.[3] However, whether therapeutic effectiveness of weight loss therapies translates to improvement in cardiometabolic profile is unknown. Dedicated randomized trials examining cardiovascular outcomes with a few weight loss agents have either been stopped prematurely or were designed to assess cardiovascular safety for non-weight loss indications.[4,5] Moreover, few trials have compared these drugs against each other. While important for clinical decision-making, little is known about the overall and comparative effects of these medications on cardiometabolic risk factors.

To address this knowledge gap, we conducted a systematic review and network-meta-analysis assessing the effect of long-term pharmacotherapy for weight loss on various facets of cardiometabolic risk, including blood glucose, cholesterol profile, blood pressure (BP), and visceral adiposity.

METHODS

Study Selection, Data Abstraction and Risk of Bias Assessment

The study was conducted using an *a priori* protocol (PROSPERO #CRD42016039486),[6] and reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analysis.[6] The search strategy was designed and conducted by an experienced medical librarian (LJP) with input from study investigators, utilizing various databases from inception to February 28, 2017. The databases included Ovid Medline, EMBASE, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials. In addition, we searched clinical trial registries (www.clinicaltrials.gov and www.clinicaltrialsregister.eu), conference proceedings and performed a recursive search of published systematic reviews. Controlled vocabulary supplemented with keywords was used to search for RCTs of drug therapy for weight loss. Details of the search strategy are shown in the eMethods.

In accordance with a previous approach,[3] we selected RCTs in (a) obese (BMI≥30kg/m^2) or overweight (BMI 25–29.9kg/m^2) adults (age >18 years), with/without excess weight-associated comorbidities (hypertension, hyperlipidemia, diabetes mellitus [DM], impaired glucose tolerance or obstructive sleep apnea), (b) treated with a pharmacological agent approved for long-term treatment of obesity (orlistat, lorcaserin, naltrexone-bupropion, liraglutide, or phentermine-topiramate) administered at the most effective approved doses for ≥1 year; (c) compared against another active agent or placebo; and (d) reporting ≥1 of pre-specified cardiometabolic outcomes besides a primary weight loss outcome (≥5% of baseline weight loss or mean weight loss in kilograms. We excluded (a) trials of short-term or non-approved pharmacological agents (such as phentermine, rimonabant, sibutramine, etc.), (b) trials in special populations (such as patients with non-alcoholic fatty liver disease or polycystic ovarian syndrome patients), and (c) observational studies. The study selection flowsheet is presented as Figure 1.

Data on study-, patient- and treatment-related characteristics were abstracted onto a standardized form, by at least two authors independently. All our study outcomes are reported on an interval scale and required abstraction of mean change from baseline, the standard deviation of the mean change, and the number of individuals for each study arm. We followed the recommended strategies for calculating standard deviation for mean change when variance estimates were not reported as a standard deviation. Risk of bias for individual studies was assessed using the Cochrane Risk of Bias assessment tool.[7]

Outcomes Assessed

Cardiometabolic risk outcomes were defined *a priori*, and included: (1) glucose profile – fasting blood glucose (mg/dL) and/or HbA1c; (2) markers of lipoprotein metabolism – LDL (mg/dL), HDL (mg/dL); (3) systolic and diastolic BP (mmHg); and (4) central adiposity, assessed using waist circumference (cm). High-sensitivity C-reactive protein, serum triglycerides and markers of insulin resistance (HOMA-IR) were considered as potential outcomes in the study protocol, but were inconsistently reported, and hence, not analyzed.

For meta-analysis, all study outcomes were abstracted as continuous changes from baseline and were obtained at the 1-year follow up. We used an intention-to-treat approach for all study outcomes. In accordance with FDA's recommendations regarding trials of weight loss agents,[8] missing values were most consistently imputed using last-observation carried forward (LOCF) imputation across studies, and was therefore used in the meta-analysis. In trials with multiple medication doses, the most effective FDA approved dose was used.

Statistical Analysis

We performed pairwise meta-analyses for all treatment comparisons using a DerSimonian and Laird random effects approach to obtain pooled effect estimates for all pairwise drug comparisons. Since all study outcomes were on a continuous scale, we reported the pooled estimates as both weighted mean difference (WMD) as well as standardized mean difference (SMD), along with their respective 95% confidence intervals (CI). We examined for statistical heterogeneity using the I^2 statistic,[9] and assessed small study effects including publication bias by examining funnel plot asymmetry and Egger's regression test.[8,10]

Next, we conducted a network meta-analysis for each study outcome incorporating data from all studies in a random-effects model. Similar to methods we have described previously,[11] we constructed a "consistency" model that accounts for heterogeneity in study effect across trials but assumes that the drug effects are not systematically different across trials.[12] In this model, while direct and indirect estimates for a comparison between two agents (A and B) may differ across studies due to heterogeneity, these differences do not represent systematic differences as a function of trial design, i.e. the estimate for comparing agents A and B comparison from two-arm trials comparing A and B are similar to those derived from three-arm trials (A-B-C). We used a frequentist approach and provide a point estimate from the network along with 95% CI from the frequency distribution of the estimate. Comparisons were reported as both WMD and SMD along with their respective 95% CI.

We performed additional sensitivity analyses. First, to account for the effect of study-level differences in baseline risk-factor on observed heterogeneity in the overall comparison, we performed random effects meta-regression analyses using the Knapp-Hartung approach for the pooled effect of pharmacological therapies on our study outcomes, and obtained measures of residual heterogeneity (residual I^2) after adjusting for specific active agent, mean patient age, proportion of women, and mean values of baseline fasting blood glucose, systolic blood pressure, low density lipoprotein, and body mass index across studies. Second, to limit the potential difference in cardiometabolic risk factors in studies where a large proportion of patients had diabetes at study entry, we performed a network meta-analysis after excluding studies in which >10% participants had diabetes. All analyses were performed using STATA 14 (College Station, TX), and level of significance was set at an alpha of 0.05.

Quality of Evidence and Clinical Relevance

We used the GRADE approach to rate the quality of evidence for estimates derived from direct meta-analysis. In this approach, direct evidence from RCTs starts at high quality and

can be downgraded based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity, I^2>70%), and/or publication bias to levels of moderate-, low-, and very low-quality.

Since a minimal clinically important difference (MCID) has not been well-defined for these cardiometabolic risk-factors, we assessed clinical relevance of observed effects based on SMD, with SMD <0.2 suggesting a minimal benefit, 0.2–0.4 suggesting modest benefit, 0.4–0.7 suggesting moderate, and >0.7 suggesting a large benefit of interventions on corresponding cardiometabolic risk-factor.[13]

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There was no funding source for this study. The corresponding author had full access to all data and was responsible for the decision to submit for publication.

RESULTS

Study Characteristics

We identified 28 RCTs of FDA-approved weight loss medications with 29,018 subjects who met current guidelines for long-term pharmacologic therapy for obesity, either with a BMI≥30kg/m^2 alone or BMI≥27kg/m^2 with ≥1 excess weight-related comorbidities (eTable 1).[14–41] The network of included studies is shown in Figure 2. The median age of study participants across studies was 46 years (range, 41 to 60) and 77% (range, 45–90) were women. The median baseline BMI was 36.1kg/m^2 (range, 32.7–42.0). The baseline cardiometabolic risk profile across studies is summarized in Table 1. The baseline median fasting blood glucose was 105.6mg/dL (interquartile range [IQR], 94.6– 161.5) and hemoglobin A1c was 7.9% (IQR, 5.7–8.1); eight trials were conducted exclusively in patients with diabetes.[18,21,26,28–30,33,34] The median baseline LDL-cholesterol was 122.7mg/dL (IQR, 112.9–137.2) and HDL-cholesterol was 46.4mg/dL (IQR, 45.5–51.3); median 34.5% (IQR, 10.3–52.5) participants had dyslipidemia. Median average systolic BP was 127.5mmHg (IQR, 121.9–135.8) and diastolic BP was 79.1mmHg (IQR, 77.5–84.2) at baseline; median 23% (IQR, 17–36) participants had hypertension at baseline. Waist circumference was 110cm (IQR, 109–115) at baseline. Additionally, 22 trials with short-term follow-up (13 orlistat, three phentermine/topiramate, one liraglutide, and one naltrexone/bupropion) (eTable 2), and six multi-arm trials comparing weight loss agents to other commonly used medications for cardiometabolic risk modification were excluded (eTable 3).

Effects on blood glucose profile

Overall, for the glucose profile outcome, obesity pharmacotherapy was associated with a modest reduction in blood glucose of 4.0mg/dL (95% CI, −4.4, −3.6; SMD −0.27), over placebo (Figure 3). Considerable heterogeneity was seen across agents (eFigure 1). On agent-specific comparisons using network meta-analysis, compared to placebo, liraglutide was associated with a moderate reduction in fasting blood glucose of 15.6mg/dL (95% CI, −23.7, −7.6; SMD −0.72) followed by orlistat (WMD, −8.0mg/dl; 95% CI, −12.2, −3.7; SMD −0.23) (Figure 4A). None of the other agents was associated with a significant decline

in fasting blood glucose. Similar effects were seen for HbA1c (eFigure 2), with the moderate reduction observed with liraglutide (WMD, −0.5%; 95% CI −0.9, −0.2; SMD, −0.54) followed by orlistat (WMD, −0.4%; 95% CI −0.6, −0.2; SMD, −0.38), and no significant differences observed with other agents. On comparison of active agents, liraglutide was superior to all other agents in lowering fasting blood glucose, though it reached statistical significance only compared to naltrexone-bupropion (eTable 4).

Effects on cholesterol profile

Pharmacotherapy for obesity had minimal effect on cholesterol profile, with very small reduction in LDL-cholesterol (WMD, −0.1mg/dL; 95% CI, −0.19, −0.01; SMD, −0.14), and a marginal increase in HDL-cholesterol (WMD, 0.1mg/dl; 95% CI, 0.07, 0.13; SMD, 0.07) (Figure 3). Considerable heterogeneity was seen across agents (eFigure 3 and 4). On agent-specific comparisons using network meta-analysis, compared to placebo, orlistat was associated with a clinically significant reduction in LDL-cholesterol, with a mean of −8.7mg/dl (95% CI, −10.7, −6.7; SMD −0.27); phentermine-topiramate was also associated with a significant reduction in LDL-cholesterol (WMD, −4.2; 95% CI, −8.2, −0.2) though the effect size was minimal (SMD, −0.15) (Figure 4B). On comparison of active agents, orlistat was superior to all other agents in lowering LDL-cholesterol, though this effect was only clinically meaningful in comparison to lorcaserin (SMD, −0.22) (eTable 5). On examining change in HDL-cholesterol as an outcome, compared to placebo, naltrexone-bupropion (WMD, 2.5mg/dL; 95% CI, 1.2, 3.8; SMD 0.40) and phentermine-topiramate (WMD, 2.2mg/dL; 95% CI, 0.4, 4.0; SMD 0.19) were associated with increase in HDL-cholesterol at 1 year (Figure 4B). In contrast, orlistat was associated with decline in HDL-cholesterol (WMD, −1.1mg/dL; 95% CI, −1.9, −0.4; SMD, −0.11) compared to placebo. On comparison of active agents, no agent was clearly superior to others in improving HDL-cholesterol; in contrast, orlistat was inferior to all other agents (eTable 5).

Effects on blood pressure

Pharmacotherapy had minimal effect on BP, with very small decline in systolic (WMD, −1.8mmHg; 95% CI, −2.0, −1.6; SMD −0.13), and diastolic BP (WMD, −2.0mmHg; 95% CI −2.0, −1.9; SMD, −0.12) (Figure 3). Considerable heterogeneity was seen across agents (eFigure 5 and 6). On agent-specific comparisons, using network meta-analysis, compared to placebo, phentermine-topiramate, liraglutide and orlistat were associated with modest reductions in systolic BP of 3.7mmHg (95% CI, −5.6, −1.9; SMD, −0.23), 2.8mmHg (95% CI −4.3, −1.2; SMD, −0.24) and 1.7mm Hg (95% CI, −2.4, −0.9; SMD, −0.19), respectively (Figure 4C). Similar changes were seen in diastolic BP (Figure 4C). On comparison of active agents, phentermine-topiramate was associated with a greater magnitude of reduction in systolic BP as compared to all other active agents (range, −2.1, −4.3mmHg), and a modestly greater reduction in diastolic BP as compared to naltrexone-bupropion (WMD, −1.5mmHg; 95% CI, −2.5, −0.4) (eTable 6).

Effects on waist circumference

Pharmacotherapy for obesity was associated with a small-moderate, 3.3cm decline in waist circumference (95% CI, −3.5, −3.1; SMD, −0.36) (Figure 3). Considerable heterogeneity was seen across agents (eFigure 7). On agent-specific comparisons, using network meta-

analysis, compared to placebo, all agents were associated with a small to moderate decrease in waist circumference – phentermine-topiramate by 7cm (95% CI −8.4, −5.6; SMD −0.49), liraglutide by 4cm (95% CI, −5.0, −3.3; SMD: −0.63), 3.5cm with naltrexone-bupropion (95% CI, −4.4, −2.6; SMD, −0.37), 2.5cm with lorcaserin (95% CI, −3.3, −1.7, SMD: −0.31) and 2.3cm with orlistat (95% CI, −2.8, −1.7; SMD: −0.26) (Figure 4D). On comparison of active agents, phentermine-topiramate was associated with higher decrease in waist circumference as compared to other agents (range −2.9, −4.8cm; SMD, −0.11, −0.23). Liraglutide was also associated with significantly greater decrease in waist circumference as compared to lorcaserin (WMD, −1.6cm; 95% CI, −2.8, −0.5; SMD, −0.32) and orlistat (WMD, −1.9cm; 95% CI, −2.8, −0.9; SMD, −0.37) (eTable 7).

Small Study Effects and Sensitivity Analyses

There was no evidence of small study effects on analysis of funnel plot symmetry. In sensitivity analyses, residual heterogeneity after accounting for patient characteristics in meta-regression analyses was lower (range 44%–82%) than pairwise analyses, but was >50% for most comparisons. Notably, between-study heterogeneity was mainly driven by differences in magnitude of the effect sizes, rather than the direction of the effect. Further, in analyses excluding 9 studies in which >10% participants had diabetes, we observed similar findings to our primary analyses (data not shown).

Quality of evidence

GRADE quality of evidence summary and its clinical relevance is summarized in Figure 3 and eTable 8. Due to high attrition rates for all trials (30%–45%), evidence was rated down for risk of bias. Overall, there was moderate certainty suggesting a moderate-large benefit of liraglutide on glucose profile and waist circumference, and moderate certainty suggesting a moderate benefit with naltrexone-bupropion on increasing HDL-cholesterol. For most other agents and outcomes, there was generally low to moderate certainty suggesting either a minimal or modest benefit of weight loss medications on cardiometabolic risk profile.

DISCUSSION

Though FDA-approved pharmacological agents for long-term treatment of obesity result in significant weight loss, with 20–54% patients achieving ≥10% weight loss,[3] they appear to have modest impact on modifying key cardiometabolic risk-factors, even one year after therapy (SMD range, 0.07 to 0.36). Most drugs were associated with improvements in waist circumference, but only marginal improvements in serum cholesterol profile and BP.

The effect of individual drugs varied substantially, and closely followed their mechanism of action. Liraglutide, an anti-diabetic, was associated with moderate improvements in glucose profile and waist circumference, with moderate confidence in estimates, with a small BP lowering and minimal effects on the cholesterol profile. Naltrexone-bupropion was associated with moderate increase in HDL-cholesterol with moderate confidence in estimates, but minimal effects on LDL-cholesterol, glucose profile and BP. Phentermine-topiramate, which induces most weight loss, was associated with largest improvement in waist circumference, but only modest improvements in the glucose profile and BP, and had

minimal effects on LDL or HDL-cholesterols. Orlistat, as a lipase inhibitor, was associated with decrease in LDL-cholesterol, but also lower HDL-cholesterol, which may be unfavorable from a cardiometabolic risk perspective. None of the drugs consistently improved all cardiometabolic risk factors and no single pharmacological agent was superior to others. However, there were drug-specific favorable effects on different components of the cardiometabolic risk profile.

The limited improvements in cardiometabolic risk with drug therapies that are otherwise effective at weight loss underscores the need for dedicated studies to assess the effects of these medications on meaningful changes in cardiovascular risk. Further, since there are drug-specific effects on important facets of cardiometabolic risk, an approach that accounts for a patient's baseline risk in the selection of drug therapies would need to be evaluated in dedicated studies.

The FDA mandates that all drugs being considered for treatment of obesity undergo long-term cardiovascular safety trials – it is crucial that these trials are designed to ensure while assessing drug safety potential long-term beneficial effect on cardiovascular risk profile are examined.[42] Only two published trials that have specifically addressed cardiovascular risk with these agents, the LIGHT trial and the LEADER trial. The LIGHT trial was designed to assess the effect of naltrexone-bupropion on BP and heart rate, particularly given concerns regarding heart rate elevations in phase III trials. However, the trial was stopped prematurely due to protocol violations.[5,43] The LEADER trial examined low-dose (1.8mg) liraglutide as a non-insulin therapy in diabetic adults with or without obesity conducted under an FDA-mandate on cardiovascular safety trials for all anti-diabetic medications. In 9,430 patients followed for 4 years, liraglutide was associated with a 13% lower rate of major adverse cardiovascular events compared to placebo.[4] Notably, patients in LEADER did not receive any behavioral or dietary counseling for weight loss, which are important components of all weight loss studies.

These findings are in contrast with more substantial cardiometabolic benefits associated with certain other contemporary weight loss therapies, particularly bariatric surgery. In both diabetic and non-diabetic obese adults, bariatric surgery is associated with robust favorable modification of cardiometabolic risk factors as well as reduction in risk of cardiovascular events.[44–50] This likely represents a combination of greater magnitude of weight loss with bariatric surgery as compared with pharmacotherapy,[51,52] and neurohormonal changes secondary to bariatric surgery,[53] such as increases in incretin or satiety hormones,[54] and improvement in biochemical, inflammatory and oxidative profiles.[55] The impact of endoscopic bariatric and metabolic therapies on cardiometabolic risk profile remains to be seen.[56]

Our study findings should be interpreted in the light of the following limitations. First, data are derived predominantly from drug-placebo comparisons with only one study comparing two active agents (liraglutide vs. orlistat) against each other.[16] Second, while we used strict inclusion and exclusion criteria to ensure comparability across trials, we cannot exclude the possibility of conceptual heterogeneity across studies. Third, there was statistical heterogeneity in the effect size in pooled analyses across therapies. However, this was

substantially lower for individual drug classes. Moreover, our sensitivity analyses suggest that some of the observed heterogeneity may be attributable to differences in baseline risk across trials. The limited reporting of cointerventions, however, limits further assessment of differences in risk-modifying therapies, such as lipid-lowering therapy across trials. Fourth, the trials had a large rate of attrition (~30%). To account for missing data, we used study-reported last observed carried forward imputation values for outcomes as suggested by the FDA guidelines for obesity pharmacotherapy. Finally, most included studies did not have a follow up beyond 1-year of drug therapy and longer studies are needed to assess the impact of adverse cardiovascular events.

In conclusion, while all currently approved pharmacological weight loss therapies are associated with significant weight loss, they appear to have minimal to modest effects on cardiometabolic risk profile of obese and overweight adults even after a year of drug therapy. Further research is needed to evaluate the long-term benefit of these medications on cardiovascular risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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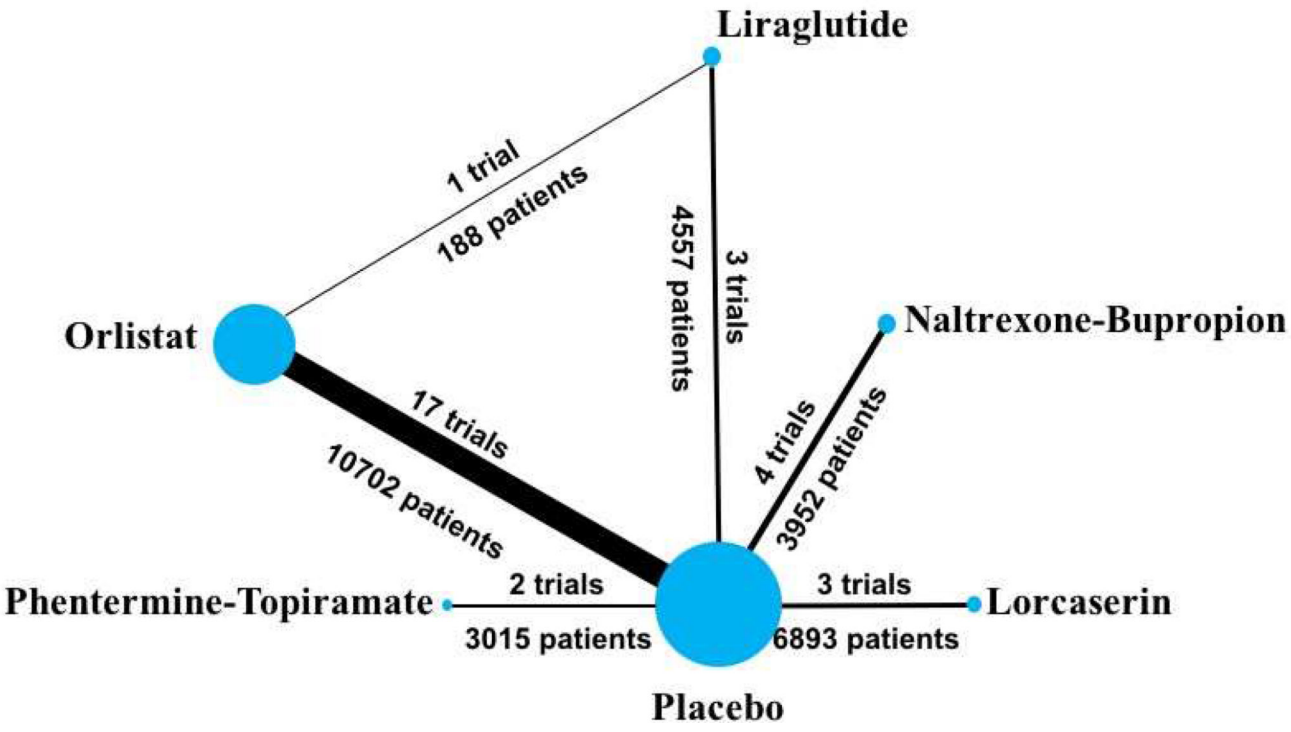

Figure 1.
Study selection flowsheet

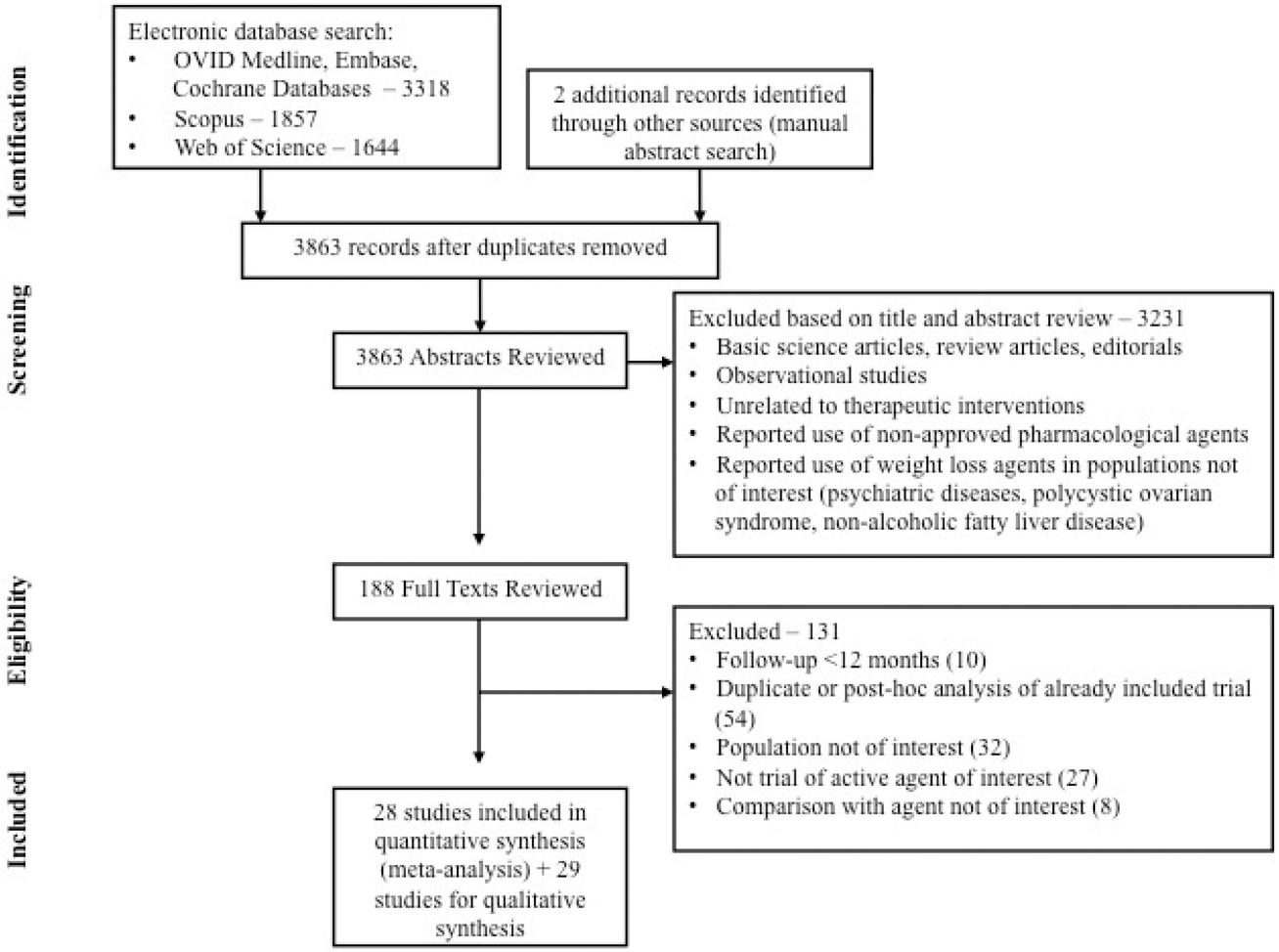

Figure 2.

Network of included studies (across outcomes). Outcomes reported in each study are included in Table 1.

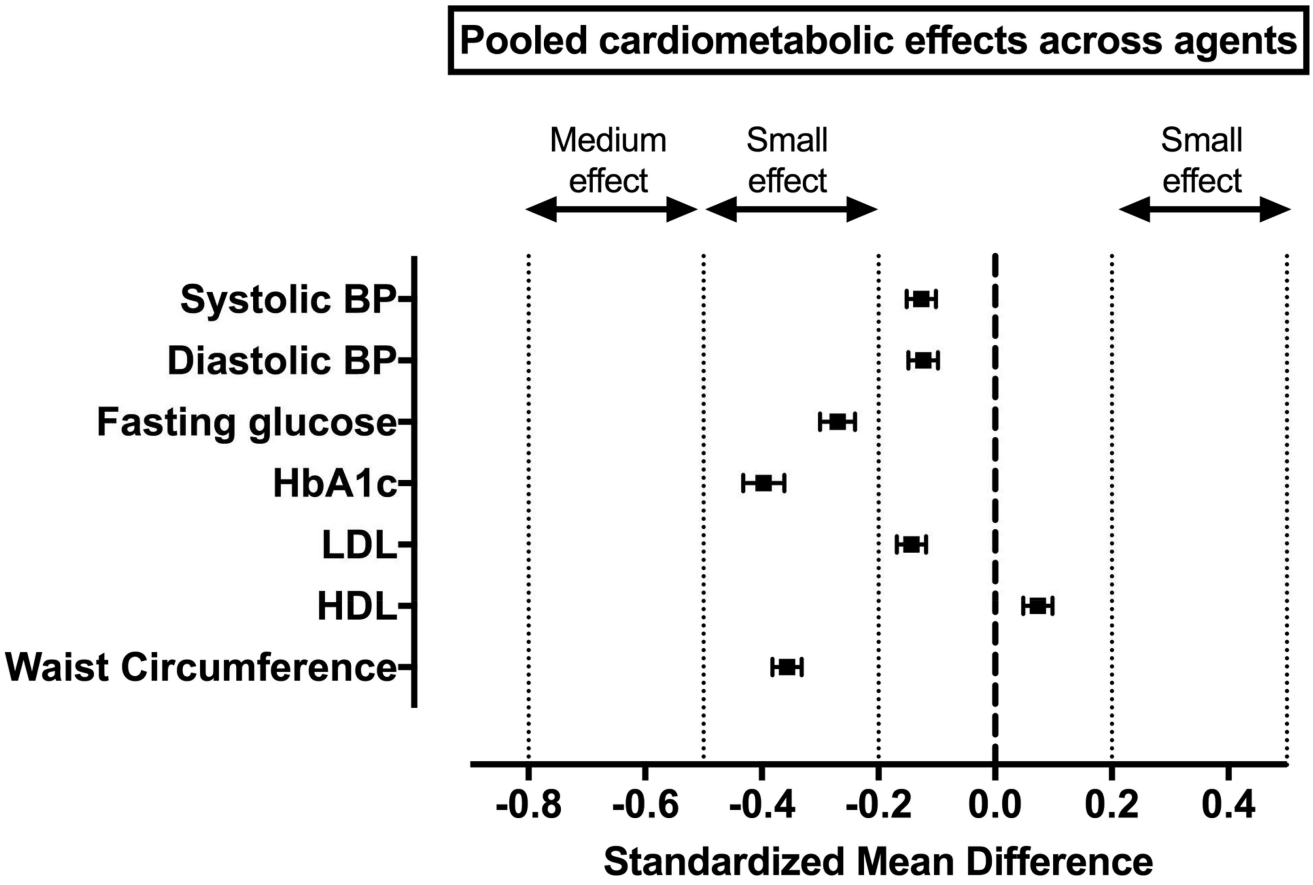

Figure 3.

Pooled effect of any pharmacologic therapy for obesity compared to placebo on each study outcome reported as standardized mean differences.

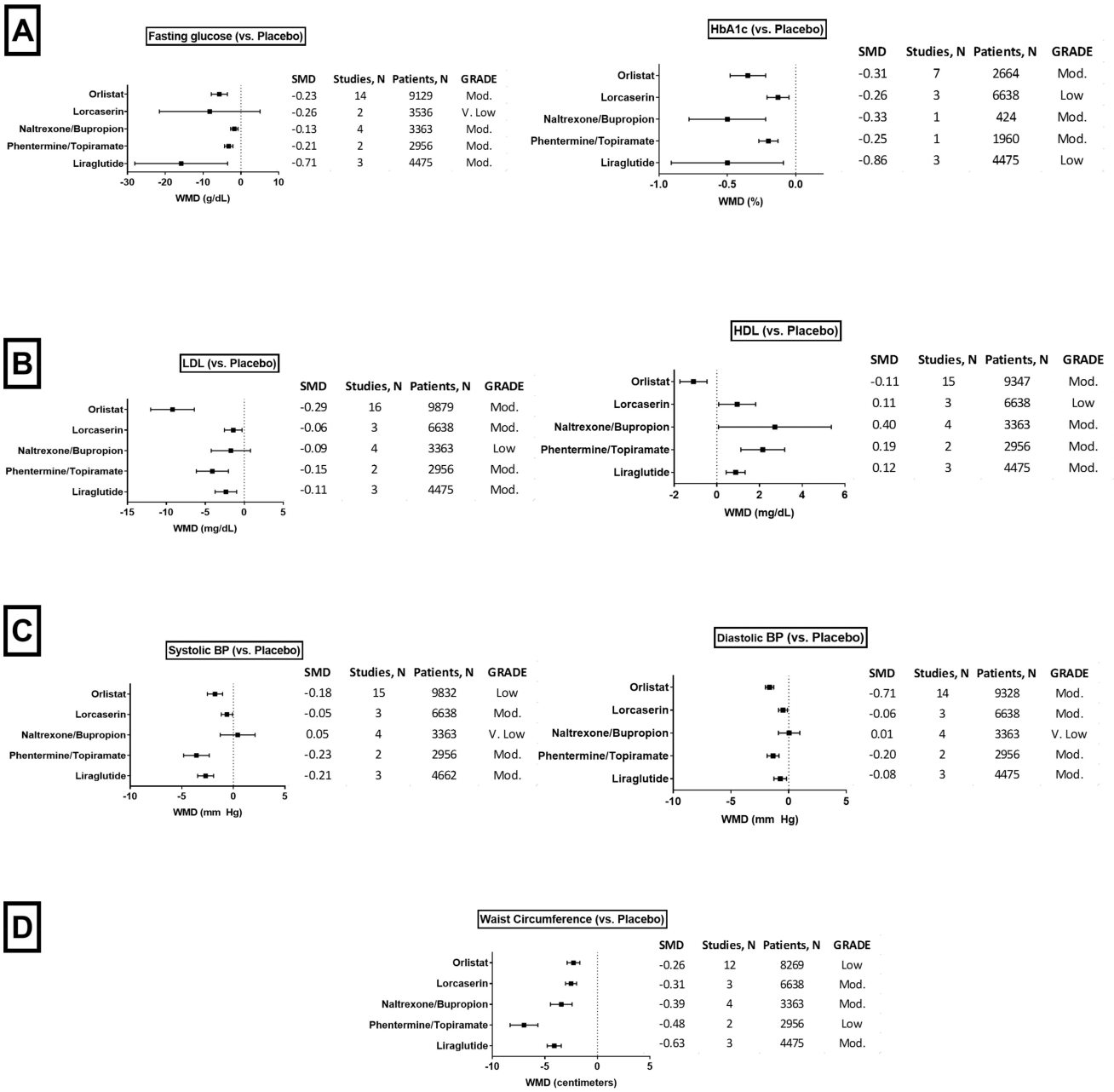

Figure 4.

Impact of individual agents against placebo after 1 year of treatment on (A) measures of blood glucose control - fasting blood glucose and hemoglobin A1c; (B) measures of cholesterol metabolism – low density lipoproteins (LDL) and high density lipoproteins (HDL); (C) blood pressure; and (D) waist circumference.

Table 1

Baseline cardiometabolic profile of study participants in randomized clinical trials for weight loss therapies

Study and year	Intervention, N	Control, N	Diabetes Mellitus, No. (%)	Hypertension, No. (%)	Dyslipidemia, No. (%)	SBP (mmHg), mean (SD)	DBP (mmHg), mean (SD)	A1c (%), mean (SD)	Fasting glucose (mg/dl), mean (SD)	LDL (mg/dl), mean (SD)	HDL (mg/dl), mean (SD)	Waist circumference (cm), mean (SD)
Orlistat vs. Placebo												
Astrup 2012[16]	95	98	I: 3 (3) C: 4 (4)	I: 16 (17) C: 27 (28)	I: 2 (2) C: 4 (4)	I: 123 (13.5) C: 124 (11.1)	I: 76.9 (7.9) C: 76.8 (8.5)	NR	NR	I: 136.1 (29.8) C: 136.5 (34.4)	I: 51.0 (12.0) C: 49.1 (10.4)	NR
Swinburn 2005[39]	170	169	I: 14 (8.2) C: 14 (8.3)	I: 26 (15.3) C: 31 (18.3)	I: 51 (30) C: 49 (29)	I: 137.3 (15.7) C: 136 (15.2)	I: 84 (9.9) C: 84.5 (9)	NR	I: 119.9 (47.2) C: 113.2 (32)	I: 138.4 (38.3) C: 134.2 (32.5)	I: 44.9 (10.8) C: 44.1 (12.8)	I: 112.4 (12.8) C: 114.8 (13.1)
Berne 2005[18]	111	109	I: 111 (100) C: 109 (100)	NR	NR	I: 145 (18.2) C: 145 (16.1)	I: 84.5 (9.7) C: 84.3 (10.0)	I: 7.6 (0.8) C: 7.6 (0.8)	I: 201.6 (46.8) C:196.2 (45.0)	I: 119.9 (38.7) C: 116 (30.9)	I: 50.3 (11.6) C: 46.4 (7.7)	I: 108 (9) C: 109 (9.3)
Torgerson 2004 (XENDOS)[40]	1650	1655	I: 0 (0) C: 0 (0)	NR	NR	C: 130.8 (15.8) I: 130.4 (15.4)	I: 82.0 (10.0) C: 82.3 (10.0)		I: 82.8 (10.8) C: 82.8 (10.8)	I: 143.1 (34.8) C: 146.9 (34.8)	I: 46.4 (11.6) C: 46.4 (11.6)	I: 115 (10.4) C: 115.4 (10.4)
Krempf 2003[31]	346	350	I: 0 (0) C: 0 (0)	NR	NR	NR	NR	NR	NR	NR	NR	I: 105.6 (0.8) C: 106.5 (0.8)
Miles 2002[33]	255	261	I: 255 (100) C: 261 (100)	NR	NR	I: 132.7 (0.9) C: 132.1 (0.9)	NR	I: 8.87 (0.07) C: 8.79 (0.07)	I: 208.8 (3.6) C: 199.8 (3.6)	I: 121.4 (2.3) C: 124.9 (2.3)	I: 37.9 (0.8) C: 37.9 (0.8)	NR
Hanefeld 2002[26]	195	188	I: 195 (100) C: 188 (100)	NR	NR	I: 148 (20.4) C: 147.9 (17.8)	I: 87.0 (10.8) C: 87.2 (10.7)	I: 8.6 (1.1) C: 8.6 (1.2)	I: 197.1 (52.7) C: 197.1 (57.1)	I: 135.3 (34.8) C: 139.2 (38.7)	I: 46.4 (11.6) C:46.4 (11.6)	I: 112.4 (12.5) C: 112.0 (12.7)
Broom 2002[19]	265	266	-	I: 54 (20.4) C: 59 (22.2)	I: 114 (43) C: 120 (45.1)	I: 141.1 (15) C: 139.2 (15.7)	I: 89 (9.7) C: 88.1 (10.1)	NR	NR	I: 146.9 (34.8) C: 146.9 (34.8)	I: 54.1 (15.5) C: 54.1 (11.6)	I: 107.8 (15.6) C: 108.6 (16.4)
Bakris 2002[17]	278	276	I: 23 (8) C: 22 (8)	I: 278 (100) C: 276 (100)	-	I: 154.2 (13.4) C: 150.8 (12.7)	I: 98.4 (37) C: 98.3 (35)	NR	NR	I: 139.2 (34.8) C: 139.2 (38.7)	I: 46.4(15.5) C: 46.4 (11.6)	I: 108.6 (12.2) C: 110.8 (12.5)
Kelley 2002[30]	274	276	I: 274 (100) C: 276 (100)	NR	NR	I: 135.1 (0.9) C: 134.9 (0.9)	I: 79.5 (0.5) C: 80.9 (0.6)	I: 9.01 (0.07) C: 8.99 (0.07)	I: 196.4 (3.6) C: 200.9 (3.6)	I: 130.3 (2.3) C: 127.6 (2.3)	I: 41.4 (0.8) C: 41.4 (0.8)	NR
Rossner 2000[36]	244	243	NR	NR	I: 20 (8.3) C: 24 (10.1)	I: 125.5 (14.9) C: 127.3 (16.1)	I: 79.5 (9.4) C: 81.2 (9.8)	NR	I: 98.5(12.2) C: 100.1 (17.6)	I: 133 (33.3) C: 137.3 (37.9)	I: 45.2(11.6) C: 45.2 (13.9)	NR
Lindgarde 2000[32]	190	186	I: 17 (8.9) C: 13 (7)	I: 74 (38.9) C: 81 (43.8)	I: 75 (39) C: 75 (40)	I: 146 (19) C: 145 (17)	I: 87 (10) C: 88 (10)	I: 5.7 (1.2) C: 5.5 (0.9)	I: 119.2(45.5) C: 114.3 (35.3)	I: 145.0 (53.4) C: 141.5 (54.5)		I: 106 (10.8) C: 106 (11)
Hauptman 2000[27]	210	212	NR	NR	NR	I: 120 (1) C: 121 (1)	I: 78 (1) C: 78 (1)	NR	I: 101.9 (0.7) C: 101.9 (0.7)	I: 122.2 (2.3) C: 122.2 (1.9)	I: 46.4 (0.8) C: 45.2 (0.8)	NR
Finer 2000[23]	114	114	I: 0 (0) C: 0 (0)	I: 6 (5.5) C: 2 (2)	I: 59 (52) C: 60 (53)	NR	NR	NR	NR	I: 141.9 (32.5) C: 141.9 (32.9)	I: 47.2 (10.8) C: 47.2 (11.2)	NR
Davidson 1999[20]	668	224	I: 26 (4) C: 10 (4.5)	I: 54 (8.2) C: 20 (9)	I: 69 (10.5) C: 12 (5.4)	NR	NR	NR	I: 101.2(0.5) C: 100.8 (0.5)	I: 142.7 (2.3) C: 123 (1.9)	I: 45.2 (0.8) C: 46.8 (0.8)	NR
Sjostrom 1998[37]	345	343	NR	NR	NR	I: 129 (0.60) C: 128 (0.60)	82.4 (0.4) 81.9 (0.4)	NR	I: 105.1(0.5) C: 104.9 (0.5)	I: 137.3 (1.2) C: 37.3 (1.2)	I: 44.5 (0.4) C: 44.9 (0.4)	I: 105.4 C: 105.9
Hollander, 1998[28]	162	159	I: 162 (100) C: 159 (100)	NR	NR	NR	NR	I: 8.05 (0.98) C: 8.2 (1.07)	I: 159.3 (30.2) C: 163.6 (33.7)	NR	NR	NR
Loracaserin vs. Placebo												
O'Neil 2012 (BLOOM-DM)[34]	256	252	I: 256 (100) C: 252 (100)	NR	NR	I: 126.6 (12.7) C: 126.5 (13.5)	I: 77.9 (8.0) C: 78.7 (7.9)	I: 8.1 (0.8) C: 8.1 (0.8)	I: 164.5 (48.1) C: 159.7 (41.7)	I: 95.0 (30.4) C: 94.6 (30.2)	I: 45.3 (11.0) C: 45.7 (12.7)	I: 115.8 (11.8) C: 113.5 (12.6)

Study and year	Intervention, N	Control, N	Diabetes Mellitus, No. (%)	Hypertension, No. (%)	Dyslipidemia, No. (%)	SBP (mmHg), mean (SD)	DBP (mmHg), mean (SD)	A1c (%), mean (SD)	Fasting glucose (mg/dl), mean (SD)	LDL (mg/dl), mean (SD)	HDL (mg/dl), mean (SD)	Waist circumference (cm), mean (SD)
Fidler 2011 (BLOSSOM)[22]	1602	1601	NR	I: 388 (24.2) C: 382 (23.9)	I: 455 (28.4) C: 438 (27.4)	I: 122.1 (12.2) C: 121.9 (11.9)	I: 78.1 (8.1) C: 78.3 (8.1)	I: 5.6 (0.4) C: 5.6 (0.4)	NR	I: 116.7 (32.1) C: 113.9 (28.6)	I: 51.8 (13.3) C: 51.4 (13.2)	I: 109.2 (12.4) C: 110.9 (12.9)
Smith 2010 (BLOOM)[38]	1595	1587	I: 0 (0) C: 0 (0)	NR	NR	I: 120.7 (0.3) C: 121.1 (0.3)	I: 76.8 (0.2) C: 77.1 (0.2)	I: 5.7 (0.0) C: 5.7 (0.0)	I: 94.3 (0.3) C: 94.1 (0.3)	I: 112.1 (0.8) C: 113.8 (0.8)	I: 54.7 (0.3) C: 55.4 (0.4)	I: 109.6 (0.3) C: 109.2 (0.3)
Naltrexone-Bupropion vs. Placebo												
Apovian 2013 (COR II)[15]	1001	495	I: 0 (0) C: 0 (0)	I: 212 (21.2) C:106 (21.4)	I: 560 (55.9) C: 263 (53.1)	I: 118.1 (10); C: 118.2 (10.5)	I: 76.8(7); C: 76.8(7)	NR	I: 94.8(11.2); C:94.2(10.4)	I: 119.8 (30.2) C: 117.1 (32.6)	I: 51.4(13.3); C:51.4(13.1)	I: 109.3 (11.9) C: 108.9 (11.7)
Hollander 2013 (COR-DM)[29]	333	169	I: 333 (100) C: 169 (100)	NR	I: 280 (83.6) C: 145 (85.3)	I: 125(11); C:124.5(11.6)	I: 77.5(7.5); C: 77.4(7.4)	I: 8.0(0.8); C: 8.0(0.9)	I: 160.3(40.3);C: 163.9(44.5)	I: 100.2 (34.2) C: 101 (33.9)	I: 46.2(10.2);C: 46.1(11.5)	I: 115.6 (12.6); C: 114.3 (12.4)
Wadden 2011 (COR-BMOD)[41]	591	202	I: 0 (0) C: 0 (0)	NR	NR	I: 116.6(10.1); C:116.7(10.9)	I: 78.3(7.0);C: 77.1(7.4)	NR	I: 92.4(10.7) C: 94.1(20.1)	I: 109.5 (27.5);C: 109.2 (27.3)	I: 53.6(13.5); C:55.3(12.9)	I: 109.3 (11.4) C: 109 (11.8)
Greenway 2010 (COR I)[25]	583	581	I: 0 (0) C: 0 (0)	I: 130 (22) C: 113 (19)	I: 284 (49) C: 288 (50)	I: 118.9(9.9);C: 119(9.8)	I: 77.1(7.2);C: 77.3(6.6)	NR	I: 94.2(12.1); C: 93.9(11.2)	I: 119.1 (32.5) C: 119.9 (34.8)	I: 51.8(13.5); C: 52.2(13.5)	I: 108.8 (11.3) C: 110 (12.2)
Phentermine-Topiramate vs. Placebo												
Allison 2012 (EQUIP)[14]	512	514	I: 0 (0) C: 0 (0)	NR	NR	I: 122.0 (11.6) C: 121.8 (11.4)	I: 77.4 (7.7) C: 77.2 (7.8)	NR	I: 93.0 (9.5) C: 93.0 (8.7)	I: 119.8 (30.1) C: 121.3 (32.0)	I: 49.8 (11.7) C: 49.5 (13.1)	I: 120.1 (14.6) C: 120.5 (13.9)
Gadde 2011 (CONQUER)[24]	995	994	I: 664 (67)[d] C: 675 (68)	I: 363 (36)[b] C: 354 (36)	NR	I: 127.9 (13.4) C: 128.9 (13.5)	I: 80.1 (9.1) C: 81.1 (9.2)	I: 5.9 (0.8) C: 5.9 (0.8)	I: 106.2 (21.6) C: 106.2 (23.4)	I: 123.7 (34.8) C: 123.7 (34.8)	I: 50.3 (15.5) C: 50.3 (15.5)	I: 113.2 (12.2) C: 113.4 (12.2)
Liraglutide vs. Placebo												
Davies 2015 (SCALE-DM)[21]	423	212	I: 423 (100) C: 212 (100)	I: 293 (69.3) C: 145 (68.4)	I: 295 (69.7) C: 126 (59.4)	I: 128.9 (13.6) C: 129.2 (13.6)	I: 79.0 (8.6) C: 79.3 (9.5)	I: 7.9 (0.8) C: 7.9 (0.8)	I: 158.4 (32.8) C: 155.5 (33.0)	I: 86.4 (35.5) C: 85.2 (39.3)	I: 45.2 (25.0) C: 45.4 (24.8)	I: 118.0 (14.4) C: 117.3 (14.0)
Pi-Sunyer 2015 (SCALE Obesity)[35]	2487	1244	I: 0 (0) C: 0 (0)	I: 850 (34.2) C: 446 (35.9)	I: 737 (29.6) C: 359 (28.9)	I: 123.0 (12.9) C: 123.2 (12.8)	I: 78.7 (8.6) C: 78.9 (8.5)	I: 5.6 (0.4) C: 5.6 (0.4)	I: 95.9 (10.6) C: 95.5 (9.8)	I: 111.6 (27.9) C: 112.2 (27.6)	I: 51.4 (26.2) C: 51.0 (26.4)	I: 115.0 (14.4) C: 114.5 (14.3)
Astrup 2012[16]	93	98	I: 4 (4) C: 4 (4)	I: 11 (12) C: 27 (28)	I: 7 (8) C: 4 (4)	I: 124 (11.3) C: 124 (11.1)	I: 77.8 (8.3) C: 76.8 (8.5)	NR	NR	I: 131.5 (30.2) C: 136.5 (34.4)	I: 49.5 (12.4) C: 49.1 (10.4)	NR
Liraglutide vs. Orlistat												
Astrup, 2012[7]	93	95	I: 4 (4) C: 3 (3)	I: 11 (12) C: 16 (17)	I: 7 (8) C: 2 (2)	I: 124 (11.3) C: 123 (13.5)	I: 77.8 (8.3) C: 76.9 (7.9)	NR	NR	I: 131.5 (30.2) C: 136.1 (29.8))	I: 49.5 (12.4) C: 51.0 (12.0)	NR

Abbreviations: A1c – glycated hemoglobin, LDL – Low density lipoproteins, HDL – high density lipoproteins, SBP – systolic blood pressure, DBP – diastolic blood pressure, WC – waist circumference