Original Investigation

Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events
A Systematic Review and Meta-analysis

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IMPORTANCE Five medications have been approved for the management of obesity, but data on comparative effectiveness are limited.

OBJECTIVE To compare weight loss and adverse events among drug treatments for obesity using a systematic review and network meta-analysis.

DATA SOURCES MEDLINE, EMBASE, Web of Science, Scopus, and Cochrane Central from inception to March 23, 2016; clinical trial registries.

STUDY SELECTION Randomized clinical trials conducted among overweight and obese adults treated with US Food and Drug Administration–approved long-term weight loss agents (orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, or liraglutide) for at least 1 year compared with another active agent or placebo.

DATA EXTRACTION AND SYNTHESIS Two investigators identified studies and independently abstracted data using a predefined protocol. A Bayesian network meta-analysis was performed and relative ranking of agents was assessed using surface under the cumulative ranking (SUCRA) probabilities. Quality of evidence was assessed using GRADE criteria.

MAIN OUTCOMES AND MEASURES Proportions of patients with at least 5% weight loss and at least 10% weight loss, magnitude of decrease in weight, and discontinuation of therapy because of adverse events at 1 year.

RESULTS Twenty-eight randomized clinical trials with 29 018 patients (median age, 46 years; 74% women; median baseline body weight, 100.5 kg; median baseline body mass index, 36.1) were included. A median 23% of placebo participants had at least 5% weight loss vs 75% of participants taking phentermine-topiramate (odds ratio [OR], 9.22; 95% credible interval [CrI], 6.63-12.85; SUCRA, 0.95), 63% of participants taking liraglutide (OR, 5.54; 95% CrI, 4.16-7.78; SUCRA, 0.83), 55% taking naltrexone-bupropion (OR, 3.96; 95% CrI, 3.03-5.11; SUCRA, 0.60), 49% taking lorcaserin (OR, 3.10; 95% CrI, 2.38-4.05; SUCRA, 0.39), and 44% taking orlistat (OR, 2.70; 95% CrI, 2.34-3.09; SUCRA, 0.22). All active agents were associated with significant excess weight loss compared with placebo at 1 year—phentermine-topiramate, 8.8 kg (95% CrI, −10.20 to −7.42 kg); liraglutide, 5.3 kg (95% CrI, −6.06 to −4.52 kg); naltrexone-bupropion, 5.0 kg (95% CrI, −5.94 to −3.96 kg); lorcaserin, 3.2 kg (95% CrI, −3.97 to −2.46 kg); and orlistat, 2.6 kg (95% CrI, −3.04 to −2.16 kg). Compared with placebo, liraglutide (OR, 2.95; 95% CrI, 2.11-4.23) and naltrexone-bupropion (OR, 2.64; 95% CrI, 2.10-3.35) were associated with the highest odds of adverse event–related treatment discontinuation. High attrition rates (30%-45% in all trials) were associated with lower confidence in estimates.

CONCLUSIONS AND RELEVANCE Among overweight or obese adults, orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, and liraglutide, compared with placebo, were each associated with achieving at least 5% weight loss at 52 weeks. Phentermine-topiramate and liraglutide were associated with the highest odds of achieving at least 5% weight loss.

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Approximately 1.9 billion adults are overweight and 600 million are obese worldwide.[1] Identifying effective long-term treatment strategies for overweight and obesity is of paramount importance. The US Food and Drug Administration (FDA) has approved 5 weight loss drugs (orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, and liraglutide) for long-term use in obese (body mass index [BMI] ≥30) or overweight (BMI ≥27) individuals with at least 1 weight-associated comorbidity (type 2 diabetes, hypertension, hyperlipidemia).[2-4] (Body mass index is calculated as weight in kilograms divided by height in meters squared.) However, there is a paucity of randomized clinical trial (RCT) evidence comparing different pharmacological interventions with each other. Data regarding relative efficacy and adverse effects of each drug can inform patients, health care practitioners, and policy makers regarding optimal medication prescription to treat obesity and overweight. In this systematic review, associations of each drug with weight loss and adverse effects were compared using a direct meta-analysis and Bayesian network meta-analysis.

Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement extension for network meta-analysis[5] and was conducted following an a priori-established protocol registered with PROSPERO (CRD42015026114).[6] Good research practices outlined in the International Society for Pharmacoeconomics and Outcomes Research report on interpreting indirect treatment comparisons and network meta-analysis for health care decision making were followed.[7] Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for network meta-analysis were used to appraise quality of evidence.[8]

Selection Criteria

Randomized clinical trials were included in this meta-analysis if they studied any of the 5 FDA-approved weight loss drugs administered at the most effective recommended doses for at least 1 year compared with either placebo or each other in obese (BMI ≥30) or overweight (BMI ≥27) adults (aged ≥18 years), with or without weight-associated comorbidities, and reported either proportion of patients achieving at least 5% weight loss or differences in mean weight loss between different study groups.

Observational studies, trials of short-term or nonapproved pharmacological agents (eg, rimonabant, sibutramine), trials comparing individual components of the approved fixed-dose combination medications (eg, naltrexone-bupropion, phentermine-topiramate), studies in special populations (patients with nonalcoholic fatty liver disease or polycystic ovary syndrome), and studies comparing an active agent with another nonapproved weight loss therapy (eg, metformin, statins) were excluded.

Search Strategy

The search strategy was designed and conducted by an experienced medical librarian with input from study investigators using various databases from inception to March 23, 2016. The databases included Ovid MEDLINE, EMBASE, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials. Clinical trial registries (http://www.clinicaltrials.gov and http://www.clinicaltrialsregister.eu), conference proceedings, and published systematic reviews were screened for additional studies. Details of the search strategy and study selection procedures are shown in the eAppendix in the Supplement.

Data Abstraction and Quality Assessment

Data on study-, patient- and treatment-related characteristics were abstracted onto a standardized form by 2 authors (R.K. and A.K.C.) independently and discrepancies were resolved by consensus in consultation with a third reviewer (S.S.). Details of the data abstraction are reported in the eAppendix in the Supplement. When trials randomized patients to different dosages of the active intervention, only data for the most effective FDA-approved dosage of the medication (orlistat, 120 mg 3 times daily; lorcaserin, 10 mg twice daily; naltrexone-bupropion, 32 mg/360 mg twice daily; phentermine-topiramate, 15 mg/92 mg once daily; and liraglutide, 3-mg subcutaneous injection daily) were used.[2-4] The risk of bias of individual studies was assessed in the context of the primary outcome using the Cochrane Risk of Bias assessment tool.[9]

Outcomes

All outcomes were assessed at 1 year of follow-up (52 [±4] weeks). The primary outcome was the proportion of patients achieving at least 5% weight loss from baseline, since this is the primary efficacy outcome mandated by the FDA in trials evaluating weight loss drugs and associated with clinically significant improvement in metabolic risk profile.[10,11] Secondary weight loss outcomes were the proportion of individuals with at least 10% weight loss and change in weight from baseline. The primary adverse event outcome was rate of discontinuation of treatment due to adverse events. Serious adverse events were not consistently defined or reported.

All data were abstracted using study-reported modified intention-to-treat analysis (ie, patients who received at least 1 dose of the drug and had 1 postrandomization weight assessment); imputation of missing values was performed in all studies using last observation carried forward (LOCF) in accordance with FDA guidelines regarding trials of weight loss agents.[10]

Quality of Evidence

The GRADE approach was used to rate the quality of evidence of estimates derived from network meta-analysis.[8] 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), and/or publication bias to levels of moderate, low, and very low quality. The rating of indirect estimates starts at the lowest rating of the 2 pairwise estimates that contribute as first-order loops to the indirect estimate but can be downgraded further for imprecision or intransitivity (dissimilarity between studies in clinical or methodological characteristics). If direct and indirect estimates were similar (ie, coherent), then the higher of their ratings was assigned to the network meta-analysis estimates.

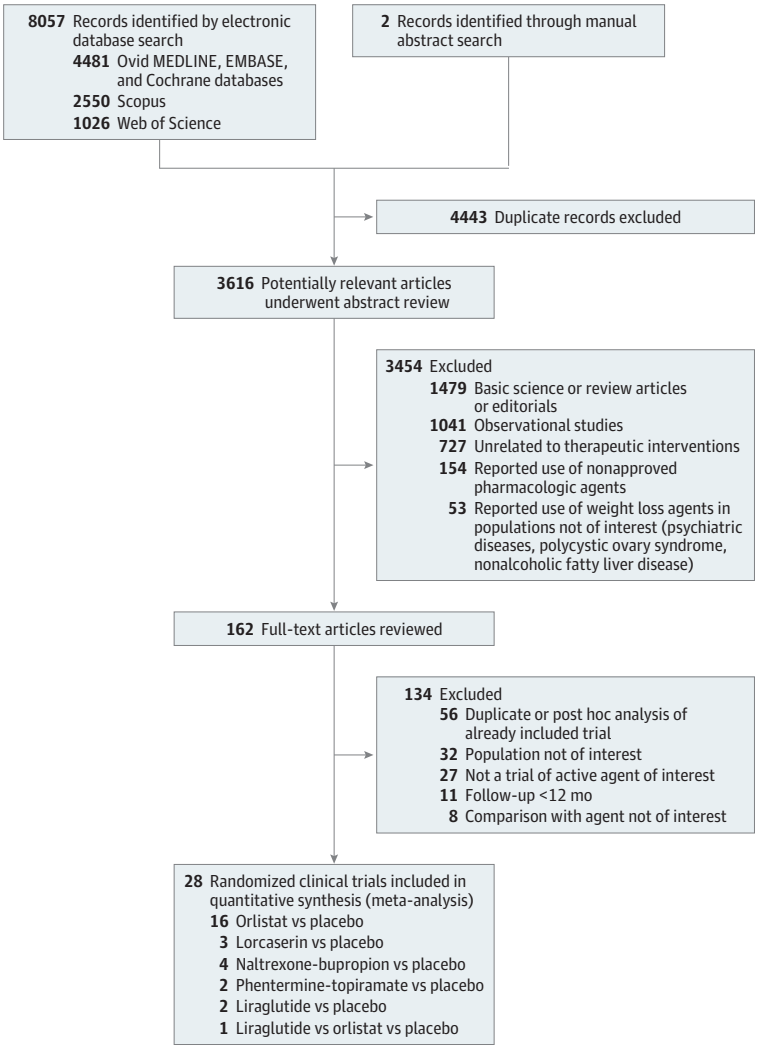
Statistical Analysis

Direct meta-analysis was performed using DerSimonian and Laird random-effects model to estimate pooled odds ratios (ORs) and 95% confidence intervals incorporating within- and between-study heterogeneity.[12] Statistical heterogeneity was assessed using the I^2 statistic, with values higher than 50% indicating substantial heterogeneity.[13] In post hoc sensitivity analyses, summary estimates were also derived using the Hartung-Knapp method to address possible type I error with the conventional DerSimonian and Laird approach.[14] Publication bias was assessed by examining funnel-plot symmetry and using the Egger regression test, with $P < .05$ suggesting publication bias.[15,16]

To incorporate indirect comparisons with direct comparisons, random-effects Bayesian network meta-analyses were conducted using Markov chain Monte Carlo methods in WinBUGS version 1.4.3 (MRC Biostatistics Unit) and methods described by Lu and Ades.[17,18] The relative ranking of agents on weight loss and adverse events outcomes was presented as their surface under the cumulative ranking (SUCRA) probabilities, which represent their likelihood of being ranked best.[19] In this study, higher SUCRA scores reflect higher associated weight loss and a lower rate of adverse events. Furthermore, using ORs derived from the network meta-analysis for placebo comparisons and median placebo response rate as the assumed control risk, absolute event rates for each intervention were estimated.[20] Details of the statistical analysis and the WinBUGS code are reported in the eAppendix in the Supplement. The level of statistical significance was set at $P < .05$ and all statistical tests were 2-sided.

Multiple sensitivity analyses were performed to assess the robustness of the findings. These were based on (1) use of an alternative statistical approach (random-effects frequentist model)[21]; (2) restricting only to studies in adults without diabetes (because antidiabetic medications may have independent weight-modifying effects); and (3) replacing trials of high-dose phentermine-topiramate with standard-dose phentermine-topiramate (7.5 mg/46 mg once daily). Additional post hoc sensitivity analyses were performed given potential bias associated with LOCF imputation

Figure 1. Study Identification and Selection



using (1) worst-case scenario analysis, wherein all patients who were randomized but did not undergo assessment of outcomes at the end of the study were considered treatment failures and (2) complete-case analysis, which limited analysis to patients who completed the entire study and underwent an assessment at the end of the trial.

Results

From a total of 3616 unique studies identified using the search strategy, 28 RCTs were included in this network meta-analysis. These included 27 two-group trials comparing active intervention to placebo (orlistat, 16 trials[22-37]; lorcaserin, 3 trials[38-40]; naltrexone-bupropion, 4 trials[41-44]; phentermine-topiramate, 2 trials[45,46]; liraglutide, 2 trials[47,48]) and 1 three-group trial comparing liraglutide and orlistat against placebo.[49] Study selection is shown in **Figure 1**. The available direct comparisons and network of trials are shown in **Figure 2** and eFigure 1 in the Supplement.

Characteristics and Quality of Included Studies

The RCTs included in the network meta-analysis are summarized in **Table 1** and **Table 2**. Overall, these 28 trials were reported between 1998 and 2015 and included 29 018 participants (the range of size of trials was 220 to 3731 participants). The primary outcome (proportion of patients achieving at least 5% weight loss at 1 year) was reported in all studies except one, which reported only weight loss on a continuous scale.[36]

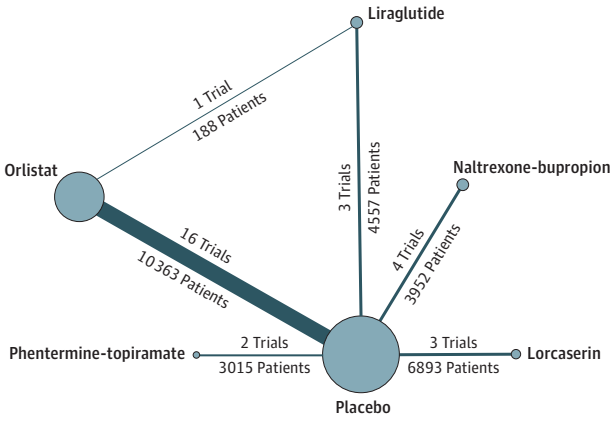
The baseline characteristics of patients included in these trials are described in eTable 1 in the Supplement. The median of average age of study participants was 45.9 years (range of average age, 40.0-59.8 years) and 74% of participants were women (range, 45%-92%). The median of average BMI of patients was 36.1 (range, 32.6-42.0) and the median of average baseline weight was 100.5 kg (range, 95.3-115.8 kg). Sixteen trials were performed exclusively in patients without diabetes (or diet-controlled diabetes), whereas 8 trials were conducted in patients with diabetes treated with pharmacological therapy. Baseline patient characteristics and prognostic factors were comparably distributed in the active and comparator groups and across different trials. In all trials, participants received standard dietary and lifestyle counseling without a structured intervention; in 1 trial, all participants received intensive behavioral modification.[44]

Overall, studies were considered to be at high risk of bias, with attrition rates of 30% to 45% in all trials. Overall and study-level quality assessments are summarized in eFigure 2 in the Supplement.

Direct Meta-analysis

Results of direct pairwise meta-analysis are summarized in **Table 3** and eFigure 3 in the Supplement. All agents were associated with higher proportions of patients achieving at least 5% and at least 10% weight loss compared with placebo. Overall, the excess weight loss compared with placebo (ie, weighted mean difference for the drug-to-placebo comparison for the respective drug) was 2.6 kg (95% CI, 2.3-2.9 kg) with orlistat, 3.2 kg (95% CI, 3.0-3.6 kg) with lorcaserin, 5.0 kg (95% CI, 4.4-5.5 kg) with naltrexone-bupropion, 8.8 kg (95% CI, 8.0-9.6 kg) with phentermine-topiramate, and 5.2 kg (95% CI, 4.9-5.6 kg) with liraglutide. All agents were more frequently discontinued because of adverse events than placebo (Table 3). Significant heterogeneity was observed for most comparisons, but the difference was primarily in the magnitude of effect size, not in the direction. In the only head-to-head comparison, liraglutide resulted in greater weight loss compared with orlistat, with no difference in adverse events.[49] In post hoc sensitivity analysis using the Hartung-Knapp method, all results were consistent (eTable 2 in the Supplement).

Figure 2. Network of Included Studies With Available Direct Comparisons for Primary Efficacy Outcome (≥5% Weight Loss)



The size of the nodes and the thickness of the edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively. The study by Swinburn et al[36] reported only continuous weight loss outcomes and is not included in this network. Network of included studies for all other outcomes is shown in eFigure 1 in the Supplement.

Network Meta-analysis—Weight Loss Outcomes

Proportion of Patients With at Least 5% and at Least 10% Weight Loss

In network meta-analysis, compared with placebo, orlistat was associated with an OR of 2.70 (95% credible interval [CrI], 2.34-3.09) , lorcaserin with an OR of 3.10 (95% CrI, 2.38-4.05), naltrexone-bupropion with an OR of 3.96 (95% CrI, 3.03-5.11), phentermine-topiramate an OR of 9.22 (95% CrI, 6.63-12.85), and liraglutide with an OR of 5.54 (95% CrI, 4.16-7.78) for achieving at least 5% weight loss (**Figure 3**). All agents were also associated with higher odds of at least 10% weight loss from baseline compared with placebo (eTable 3 in the Supplement). Placebo was associated with a 23% median rate of achieving at least 5% weight loss while phentermine-topiramate was associated with achieving at least 5% weight loss in an estimated 75% of participants, liraglutide in an estimated 63%, naltrexone-bupropion in an estimated 55%, lorcaserin in an estimated 49%, and orlistat in an estimated 44% (eTable 4 in the Supplement). Similarly, with a 9% median rate of achieving at least 10% weight loss in placebo-treated patients, phentermine-topiramate was associated with achieving at least 10% weight loss in an estimated 54% of participants, liraglutide in an estimated 34%, naltrexone-bupropion in an estimated 30%, lorcaserin in an estimated 25%, and orlistat in an estimated 20%.

Table 1. Characteristics of Included Randomized Clinical Trials Comparing Orlistat vs Placebo for Weight Loss[a]

	Total Enrolled/mITT/Completers		Cointerventions			Outcomes of Interest Reported			
Source/Period	Intervention	Control	Diet	Exercise	Behavior	Mean Weight Change	Proportion With ≥5% Weight Loss	Proportion With ≥10% Weight Loss	Treatment Withdrawals Due to Adverse Events
Astrup et al,[49] 2012 (Europe)/2007-2009	95/67/45	98/67/47	500-kcal/d deficit[b]	Brisk walking ≥150 min/wk	Yes	✓	✓	✓	✓
Swinburn et al,[36] 2005 (Australia and New Zealand)	70/170/132	169/169/137	Reduce fat intake (40 g/d)	Moderate, 30 min/d	Yes	✓			✓
Berne,[23] 2005 (Sweden)/1999-2002	111/111/96	109/109/94	600-kcal/d deficit	Moderate, 30 min/d	Yes		✓	✓	✓
Torgerson et al,[37] 2004 (Sweden)/1997-2002	1650/1640/850	1655/1637/564	800-kcal/d deficit	Moderate, walk 1 extra km/d	Yes		✓	✓	✓
Krempf et al,[31] 2003 (France)	346/346/224	350/350/201	20% energy reduction		No	✓	✓	✓	✓
Miles et al,[33] 2002 (US and Canada)	255/250/165	261/254/146	600-kcal/d deficit	Nonspecific increase	Yes	✓	✓	✓	✓
Hanefeld and Sachse,[27] 2002 (Germany)	195/189/133	188/180/131	600-kcal/d deficit		No	✓	✓		✓
Broom et al,[24] 2002 (UK)	265/265/186	266/266/161	600-kcal/d deficit		No	✓	✓	✓	✓
Bakris et al,[22] 2002 (US)	278/267/160	276/265/106	600-kcal/d deficit	Nonspecific increase	No	✓	✓		✓
Kelley et al,[30] 2002 (US)	274/266/129	276/269/141	600-kcal/d deficit	Nonspecific increase	Yes	✓	✓	✓	✓
Rossner et al,[34] 2000 (Europe)	244/242/181	243/237/158	600-kcal/d deficit		No	✓	✓	✓	✓
Lindgarde,[32] 2000 (Sweden)	190/190/159	186/186/164	600-kcal/d deficit	Moderate, 30 min/d	Yes	✓	✓	✓	✓
Hauptman et al,[28] 2000 (US)	210/210/151	212/212/122	600-kcal/d deficit	Moderate, 20-30 min/d (3-5 times/wk)	Yes	✓	✓	✓	✓
Finer et al,[26] 2000 (UK)	114/110/66	114/108/73	600-kcal/d deficit (reduced by further 300 kcal at 24 wk)		No	✓	✓	✓	✓
Davidson et al,[25] 1999 (US)/1992-1995	668/657/458	224/223/133	Energy-deficient diet (30% energy from fat)	Brisk walking, 20-30 min/d (3-5 times/wk)	Yes	✓	✓	✓	✓
Sjostrom et al,[35] 1998 (Europe)	345/343/284	343/340/260	600-kcal/d deficit (reduced by further 300 kcal at 24 wk)		No		✓	✓	✓
Hollander et al,[29] 1998 (US)	162/162/139	159/159/115	Energy-deficient diet (30% energy from fat)		No	✓	✓	✓	

Abbreviation: mITT, modified intention to treat (last-observation-carried-forward analysis).

[a] All trials were randomized, double-blind, placebo-controlled, multicenter studies except Broom et al,[25] a single-center study. All trials had follow-up through 52 weeks.

[b] Baseline calculated using World Health Organization equations; 30% of energy from fat, 20% from protein, and 50% from carbohydrate.

Table 2. Characteristics of Randomized Clinical Trials Comparing Lorcaserin, Naltrexone-Bupropion, Phentermine-Topiramate, and Liraglutide vs Placebo for Weight Loss[a]

	Total Enrolled/mITT/Completers		Cointerventions			Outcomes of Interest Reported			
Source/Period	Intervention	Control	Diet	Exercise	Behavior	Mean Weight Change	Proportion With ≥5% Weight Loss	Proportion With ≥10% Weight Loss	Treatment Withdrawals Due to Adverse Events
Lorcaserin vs Placebo									
O'Neil et al,[39] 2012 (US)/2007-2010	256/251/169	252/248/157	600-kcal/d deficit[b]	Moderate, 30 min/d	Yes	✓	✓	✓	✓
Fidler et al,[38] 2011 (US)/2007-2009	1602/1561/917	1601/1541/834	600-kcal/d deficit[b]	Moderate, 30 min/d	Yes	✓	✓	✓	✓
Smith et al,[40] 2010 (US)/2006-2009	1595/1538/883	1587/1499/676	600-kcal/d deficit[b]	Moderate, 30 min/d	Yes	✓	✓	✓	✓
Naltrexone-Bupropion vs Placebo									
Apovian et al,[41] 2013 (US)/2007-2009	1001/826/538	495/456/267	500-kcal/d deficit	Nonspecific increase	Yes	✓	✓	✓	✓
Hollander et al,[43] 2013 (US)/2007-2009	333/265/175	169/159/100	500-kcal/d deficit	Brisk walking, 30 min/d	Yes		✓	✓	✓
Wadden et al,[44] 2011 (US)/2007-2009	591/482/301	202/193/106	Graded energy balance[c]	Moderate, 180 min/wk, increasing to 360 min/wk	Yes		✓	✓	✓
Greenway et al,[42] 2010 (US)/2007-2009	583/471/296	581/511/290	500-kcal/d deficit[b]	Nonspecific increase	Yes	✓	✓	✓	✓
Phentermine-Topiramate vs Placebo									
Allison et al,[45] 2012 (US)/2007-2009	512/498/301	514/498/241	500-kcal/d deficit[b]	Nonspecific increase	Yes		✓	✓	✓
Gadde et al,[46] 2011 (US)/2007-2009	995/981/733	994/979/616	500-kcal/d deficit[b]		Yes	✓	✓	✓	✓
Liraglutide vs Placebo									
Davies et al,[47] 2015/2011-2013[d]	423/412/324	212/211/140	500-kcal/d deficit[b,e]	Brisk walking ≥150 min/wk	Yes	✓	✓	✓	✓
Pi-Sunyer et al,[48] 2015/2011-2013[d]	2487/2437/1789	1244/1225/801	500-kcal/d deficit[b,e]	Brisk walking ≥150 min/wk	Yes	✓	✓	✓	✓
Astrup et al,[49] 2012/2007-2009[d]	93/72/47	98/67/47	500-kcal/d deficit[b,e]	Brisk walking ≥150 min/wk	Yes	✓	✓	✓	✓
Liraglutide vs Orlistat									
Astrup et al,[49] 2012/2007-2009[d]	93/72/47	95/67/45	500-kcal/d deficit[b,e]	Brisk walking ≥150 min/wk	Yes	✓	✓	✓	✓

Abbreviation: mITT, modified intention to treat (last-observation-carried-forward analysis).

[a] All trials were randomized, double-blind, placebo-controlled, multicenter studies. Trials had follow-up through 52 weeks with the exception of the following, which went to 56 weeks: Apovian et al, Hollander et al, Wadden et al, and Greenway et al (all naltrexone-bupropion vs placebo); and Davies et al (liraglutide vs placebo).

[b] Baseline calculated using World Health Organization equations.

[c] Participants: weight ≤249 lb, 1200 kcal/d; weight 250-299 lb, 1500 kcal/d; weight 300-349 lb, 1800 kcal/d; weight ≥350 lb, 2000 kcal/d. Balanced deficit diet: approximately 15%-20% of energy from protein, ≤30% energy from fat, and the remainder from carbohydrate.

[d] International trial.

[e] Thirty percent of energy from fat, 20% from protein, and 50% from carbohydrate.

Table 3. Summary of Direct Meta-analysis for All Weight Loss and Adverse Event Outcomes

Pharmacological Intervention	No. of Studies	Active Intervention		Control (Placebo Unless Otherwise Noted)		OR or Weighted Mean Difference, kg (95% CI)
		No. With Event	Total No.	No. With Event	Total No.	
≥5% Weight Loss						
Orlistat	16	3140	5315	1694	4694	2.69 (2.36 to 3.07)
Lorcaserin	3	1562	3350	729	3288	3.09 (2.49 to 3.83)
Naltrexone-bupropion	4	1081	2044	274	1319	3.90 (2.91 to 5.22)
Phentermine-topiramate	2	1019	1479	290	1477	9.10 (7.68 to 10.78)
Liraglutide	3	vs Placebo: 1798 vs Orlistat: 53	2921 72	Placebo: 380 Orlistat: 29	1503 67	5.09 (4.07 to 6.37) 3.66 (1.79 to 7.46)
≥10% Weight Loss						
Orlistat	14	1520	4859	684	4249	2.41 (2.08 to 2.78)
Lorcaserin	3	742	3350	276	3288	3.17 (2.53 to 3.97)
Naltrexone-bupropion	4	599	2044	112	1319	4.11 (2.80 to 6.05)
Phentermine-topiramate	2	702	1479	109	1477	11.34 (9.10 to 14.13)
Liraglutide	3	vs Placebo: 930 vs Orlistat: 27	2921 72	Placebo: 146 Orlistat: 9	1503 67	4.36 (3.61 to 5.26) 3.87 (1.65 to 9.04)
Mean Weight Loss in Excess of Placebo[a]						
Orlistat	14		3391		2777	−2.63 (−2.94 to −2.32)[b]
Lorcaserin	3		3350		3288	−3.25 (−3.55 to −2.95)[b]
Naltrexone-bupropion	2		1297		967	−4.95 (−5.54 to −4.36)[b]
Phentermine-topiramate	1		981		979	−8.80 (−9.62 to −7.98)[b]
Liraglutide	3		2921 72		1503 67	−5.24 (−5.60to−4.87)[b] −3.90 (−5.18 to −2.62)[b]
Discontinuation of Therapy Due to Adverse Events						
Orlistat	16	439	5323	224	4704	1.84 (1.55 to 2.18)
Lorcaserin	3	250	3350	190	3288	1.40 (0.96 to 2.03)
Naltrexone-bupropion	4	501	2044	175	1319	2.60 (2.15 to 3.14)
Phentermine-topiramate	2	274	1479	132	1477	2.32 (1.86 to 2.89)
Liraglutide	3	vs Placebo: 292 vs Orlistat: 7	2921 72	Placebo: 57 Orlistat: 2	1503 67	2.82 (2.10 to 3.77) 3.50 (0.70 to 17.49)

Abbreviation: OR, odds ratio.

[a] Continuous outcome; event rate not applicable.

[b] Weighted mean difference (or excess weight loss vs placebo).

Figure 3. Comparison of Weight Loss and Adverse Events With Pharmacological Weight Loss Agents in Network Meta-analysis

Odds ratio (95% CrI) for discontinuation due to adverse events	Odds ratio (95% CrI) for achieving at least 5% weight loss					
	Phentermine-topiramate	1.67 (1.03-2.56)	2.33 (1.54-3.59)	2.98 (1.95-4.54)	3.42 (2.40-4.91)	9.22 (6.63-12.85)
	0.78 (0.48-1.20)	Liraglutide	1.4 (0.96-2.18)	**1.78 (1.22-2.78)**	**2.06 (1.51-2.96)**	**5.54 (4.16-7.78)**
	0.87 (0.59-1.25)	1.11 (0.74-1.72)	Naltrexone-bupropion	1.28 (0.87-1.84)	**1.47 (1.09-1.96)**	**3.96 (3.03-5.11)**
	1.71 (1.14-2.49)	**2.2 (1.43-3.39)**	**1.97 (1.38-2.76)**	Lorcaserin	1.15 (0.86-1.55)	**3.1 (2.38-4.05)**
	1.25 (0.88-1.76)	**1.6 (1.10-2.40)**	**1.44 (1.07-1.95)**	0.73 (0.54-1.02)	Orlistat	**2.7 (2.34-3.09)**
	2.29 (1.71-3.06)	**2.95 (2.11-4.23)**	**2.64 (2.1-3.35)**	**1.34 (1.05-1.76)**	**1.84 (1.53-2.21)**	Placebo

Summary estimate represents odds ratio of achieving at least 5% weight loss (light gray background) and discontinuation due to adverse events (light blue background). Agents are ordered by rankings for the 5% weight loss outcome. Odds ratio for comparisons are in the cell in common between the column-defining and row-defining treatment. For weight loss outcome, row treatment is compared with column treatment (ie, column treatment is reference). For adverse event outcome, column treatment is compared with row treatment (ie, row treatment is reference). Numbers in parentheses indicate 95% credible intervals (95% CrIs). Numbers in bold represent statistically significant results.

Network meta-analysis suggested that phentermine-topiramate, 15 mg/92 mg once daily, was associated with the highest probability of achieving at least 5% weight loss (SUCRA, 0.95), followed by liraglutide (SUCRA, 0.83), naltrexone-bupropion (SUCRA, 0.60), lorcaserin (SUCRA, 0.39), and orlistat (SUCRA, 0.22) (**Figure 4**). Similarly, phentermine-topiramate was associated with the highest probability of achieving at least 10% weight loss (SUCRA, 0.99), followed by liraglutide (SUCRA, 0.71), naltrexone-bupropion (SUCRA, 0.64), lorcaserin (SUCRA, 0.44), and orlistat (SUCRA, 0.16).

Weight Loss in Excess of Placebo

In network meta-analysis, all active agents were associated with significant excess weight loss vs placebo at 1 year—orlistat, 2.6 kg (95% CrI, −3.04 to −2.16 kg); lorcaserin, 3.2 kg (95% CrI, −3.97 to −2.46 kg); naltrexone-bupropion, 5.0 kg (95% CrI, −5.94 to −3.96 kg); phentermine-topiramate, 8.8 kg (95% CrI, −10.20 to −7.42 kg); and liraglutide, 5.3 kg (95% CrI, −6.06 to −4.52 kg). Network meta-analysis also suggested that phentermine-topiramate, 15 mg/92 mg once daily, was associated with significant excess weight loss compared with all active agents (change vs orlistat, 6.2 kg; vs lorcaserin, 5.6 kg; vs naltrexone-bupropion, 3.9 kg; and vs liraglutide, 3.5 kg) (eTable 3 in the Supplement).

Sensitivity Analysis

Results from multiple sensitivity analyses are reported in eTables 5-8 in the Supplement. Overall, the results were similar to the main analysis for the primary outcome in sensitivity analyses based on (1) alternative statistical model (frequentist approach using a random-effects inconsistency model, worst-case scenario, complete-case analysis); (2) restricting to only studies in adults without diabetes; and (3) replacing trials of high-dose phentermine-topiramate with standard-dose phentermine-topiramate (7.5 mg/46 mg once daily).

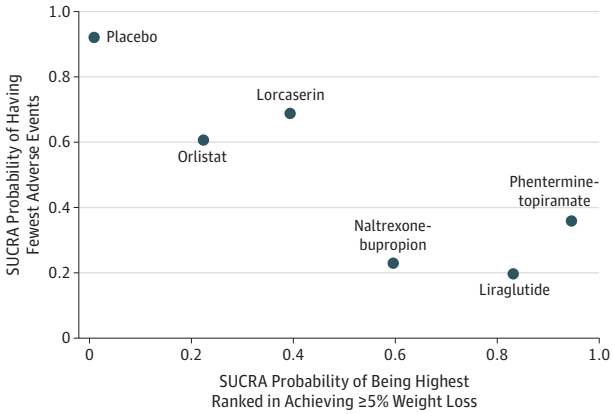
Network Meta-analysis—Adverse Event Outcome

In network meta-analysis, compared with placebo, all active agents had 1.3 to 2.9 higher odds of being associated with discontinuation due to adverse events (Figure 3). Compared with placebo, lorcaserin was associated with the lowest odds of being discontinued because of adverse events (OR, 1.34; 95% CrI, 1.05-1.76; SUCRA, 0.61), whereas liraglutide (OR, 2.95; 95% CrI, 2.11-4.23; SUCRA, 0.20) and naltrexone-bupropion (OR, 2.64; 95% CrI, 2.10-3.35; SUCRA, 0.23) were associated with the highest odds of being discontinued because of adverse events (Figure 4 and eTable 4 in the Supplement). Details of the most commonly observed adverse events and reported reasons for discontinuation are shown in eTable 9 in the Supplement.

Publication Bias and Network Coherence

There was no evidence of publication bias, either qualitatively based on funnel-plot asymmetry (eFigure 4 in the Supplement) or quantitatively (Egger regression test, $P > .05$ for all comparisons), although the number of studies included in each comparison was very small. There were no significant differences between direct and indirect estimates in the only closed loop that allowed assessment of network coherence (placebo-orlistat-liraglutide). Visual inspection of trace plots and evaluation of the Monte Carlo error and the Brooks-Gelman-Rubin statistic suggested adequacy of burn-in and convergence.[50] Values of the total residual deviance suggested good model fit.

Figure 4. SUCRAs for Weight Loss and Adverse Event Outcomes



	Placebo	Orlistat	Lorcaserin	Naltrexone-bupropion	Liraglutide	Phentermine-topiramate
Weight loss rank (95% CrI)	6 (6-6)	5 (4-5)	4 (3-5)	3 (2-4)	2 (2-3)	1 (1-1)
Adverse event rank (95% CrI)	1 (1-1)	3 (2-4)	2 (2-3)	5 (5-6)	6 (4-6)	4 (3-6)

Surface under the cumulative rankings (SUCRAs) between 0 and 1 represent the probability of being ranked highest. For the weight loss outcomes, higher score corresponds to higher proportion achieving at least 5% weight loss with a particular therapy. For the adverse event outcome, higher scores reflect lower probability of discontinuation due to adverse events. The median ranks on both weight loss and adverse event rates (rank 1 through 6 on each scale) are tabulated along with their corresponding 95% credible intervals (95% CrIs).

Quality of Evidence

Given high attrition rates for all trials (30%-45%), evidence was downgraded for risk of bias. Although several comparisons had statistically significant heterogeneity, the difference was primarily in the magnitude of effect size, not in the direction of effect, and hence, evidence was not downgraded for inconsistency. On applying GRADE to findings from the network meta-analysis combining direct and indirect evidence, there was moderate-quality evidence for all agents being associated with higher odds of achieving at least 5% weight loss compared with placebo. In comparing different drugs against each other, there was moderate-quality evidence for phentermine-topiramate being associated with higher odds of achieving weight loss compared with all other drugs. There was also moderate-quality evidence for liraglutide being associated with higher odds of achieving weight loss compared with orlistat and lorcaserin and low-quality evidence for liraglutide being associated with higher odds of achieving weight loss compared with naltrexone-bupropion (which was downgraded for imprecision and risk of bias) (eTable 10 in the Supplement).

Discussion

In this systematic review and network meta-analysis, direct and indirect evidence from 28 RCTs in 29 018 overweight and obese patients was combined to compare the association of each drug with relative weight loss and adverse events. The study has several key findings. First, with at least 1 year of treatment, orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, and liraglutide are all associated with higher odds of achieving weight loss compared with placebo, with moderate confidence in estimates. Second, phentermine-topiramate was associated with higher odds of achieving weight loss of at least 5% and weight loss of at least 10% compared with all other active agents, with moderate confidence in estimates, and there was no difference in the odds of adverse event–related drug discontinuation among phentermine-topiramate, liraglutide, and naltrexone-bupropion. Third, liraglutide was associated with higher odds of weight loss of at least 5% and weight loss of at least 10% compared with orlistat, lorcaserin, and naltrexone-bupropion, with low to moderate confidence in estimates, but was associated with higher odds of discontinuation due to adverse events.

The US Preventive Services Task Force recommends referral of all obese adults to intensive, multicomponent interventions including behavioral interventions, pharmacological therapies, and surgical weight loss procedures.[51] The Endocrine Society also suggests the use of approved weight loss medications for long-term weight maintenance, to ameliorate comorbidities, and to enhance adherence to behavior changes.[52] However, there are no current recommendations to guide clinicians regarding choice of individual drugs.

The present study found moderate-quality evidence for phentermine-topiramate being associated with higher odds of achieving predefined thresholds of clinically meaningful weight loss compared with other currently approved agents. The odds of discontinuation of therapy due to medication-related adverse events was not different for phentermine-topiramate, liraglutide, and naltrexone-bupropion. While lorcaserin and orlistat were associated with lower rates of adverse events, they were also associated with lower rates of achieving all weight loss outcomes. Besides weight loss, treatment decisions may also be driven by coexisting medical conditions, which may either favor or preclude the use of specific agents.[2] For example, liraglutide may be a more appropriate agent in people with diabetes because of its glucose-lowering effects.[47] Conversely, naltrexone-bupropion in patients with chronic opiate or alcohol dependence may be associated with neuropsychiatric complications.[2] Ultimately, given the differences in safety, efficacy, and response to therapy, the ideal approach to weight loss should be highly individualized, identifying appropriate candidates for pharmacotherapy, behavioral interventions, and surgical interventions.[53] Historically, concerns regarding the long-term safety profile of pharmacotherapy for weight loss have limited their clinical use, particularly among medications with significant adrenergic actions (eg, sibutramine) or central appetite-suppressing actions (eg, rimonabant).[54] Short-term clinical trials may not provide comprehensive information on the long-term safety of these agents, and prospective postmarketing surveillance studies are warranted.

This study has limitations. First, there was a paucity of direct comparative studies. Four of the 5 studied agents received approval from the FDA within the last 3 years, and because there is no established standard weight loss agent against which a new agent needs to be compared for approval, there is a paucity of head-to-head trials. Second, the biggest threat to validity of the results of any meta-analysis is conceptual heterogeneity—ie, considerable differences among trials in patient characteristics, studied interventions, cointerventions/background therapy, outcome assessment, or study design—which can limit the comparability of trials. Strategies to limit the effect of conceptual heterogeneity included strict inclusion and exclusion criteria and the use of multiple sensitivity analyses to assess the robustness of the results. Cointerventions in the studies, including diet and exercise recommendations and behavioral modification, were similar, although rigor of implementation and adherence by trial participants was not routinely measured, and their association with the relative efficacy of active interventions is unclear. Third, ranking probabilities may be affected by unequal numbers of trials per comparison, sample size of individual studies, network configuration, and effect sizes among treatments and should be interpreted with caution. Finally, all included trials had a high rate of attrition. Although statistical tools allowed interpretation of these data (using an LOCF imputation as suggested by the FDA guidelines), there are unaddressed concerns regarding the long-term effect of weight loss agents in a clinical setting.

Conclusions

Among overweight or obese adults, orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, and liraglutide, compared with placebo, were each associated with achieving at least 5% weight loss at 52 weeks. Phentermine-topiramate and liraglutide were associated with the highest odds of achieving at least 5% weight loss.

ARTICLE INFORMATION

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