Meta-Analysis: Pharmacologic Treatment of Obesity

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Background: **In response to the increase in obesity, pharmacologic treatments for weight loss have become more numerous and more commonly used.**

Purpose: **To assess the efficacy and safety of weight loss medications approved by the U.S. Food and Drug Administration and other medications that have been used for weight loss.**

Data Sources: **Electronic databases, experts in the field, and unpublished information.**

Study Selection: **Up-to-date meta-analyses of sibutramine, phentermine, and diethylpropion were identified. The authors assessed in detail 50 studies of orlistat, 13 studies of fluoxetine, 5 studies of bupropion, 9 studies of topiramate, and 1 study each of sertraline and zonisamide. Meta-analysis was performed for all medications except sertraline, zonisamide, and fluoxetine, which are summarized narratively.**

Data Extraction: **The authors abstracted information about study design, intervention, co-interventions, population, outcomes, and methodologic quality, as well as weight loss and adverse events from controlled trials of medication.**

Data Synthesis: **All pooled weight loss values are reported relative to placebo. A meta-analysis of sibutramine reported a mean difference in weight loss of 4.45 kg (95% CI, 3.62 to 5.29 kg) at 12 months. In the meta-analysis of orlistat, the estimate of the mean weight loss for orlistat-treated patients was 2.89 kg (CI, 2.27 to 3.51 kg) at 12 months. A recent meta-analysis of phentermine and diethylpropion reported pooled mean differences in weight loss at 6 months of 3.6 kg (CI, 0.6 to 6.0 kg) for phentermine-treated patients and 3.0 kg (CI, −1.6 to 11.5 kg) for diethylpropion-treated patients. Weight loss in fluoxetine studies ranged from 14.5 kg of weight lost to 0.4 kg of weight gained at 12 or more months. For bupropion, 2.77 kg (CI, 1.1 to 4.5 kg) of weight was lost at 6 to 12 months. Weight loss due to topiramate at 6 months was 6.5% (CI, 4.8% to 8.3%) of pretreatment weight. With one exception, long-term studies of health outcomes were lacking. Significant side effects that varied by drug were reported.**

Limitations: **Publication bias may exist despite a comprehensive search and despite the lack of statistical evidence for the existence of bias. Evidence of heterogeneity was observed for all meta-analyses.**

Conclusions: **Sibutramine, orlistat, phentermine, probably diethylpropion, bupropion, probably fluoxetine, and topiramate promote modest weight loss when given along with recommendations for diet. Sibutramine and orlistat are the 2 most-studied drugs.**

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Obesity has been defined as excess body fat relative to lean body mass (1) and, in humans, is the result of interactions of the environment with multiple genes. The age-adjusted prevalence of obesity was 30.5% in 1999–2000 (2). Although it is difficult to precisely estimate the change in prevalence of obesity over time because of changing definitions, nearly all clinical authorities agree that obesity is reaching epidemic proportions (2–13). Obesity is currently defined as a body mass index (BMI) of 30 kg/m^2 or greater. Individuals whose BMI falls between 25 kg/m^2 and 29.9 kg/m^2 are considered overweight. Attempts to meet the body weight goal of the Healthy People 2000 initiative (7)—to reduce the prevalence of overweight among adults to less than 20% of the population—did not succeed. Still, many Americans are trying. According to a national survey (14), about 40% of women and 25% of men reported that they were currently trying to lose weight. However, most weight loss attempts consist of 6 months of loss followed by gradual regain to baseline (15).

The health consequences of obesity include some of the most common chronic diseases in our society. Obesity is an independent risk factor for heart disease (16). Type 2 diabetes mellitus, hypertension and stroke, hyperlipidemia, osteoarthritis, and sleep apnea are all more common in obese individuals (17–19). A recent prospective study involving 900 000 U.S. adults reported that increased body weight was associated with increased death rates for all cancer combined and for cancer at multiple specific sites (20). Adult weight gain is associated with increased risk for breast cancer in postmenopausal women (21). Weight loss of 5% to 10% can be associated with marked reductions in the risk for these chronic diseases (22). In the Diabetes Prevention Program, weight loss of about 5% to 6% among persons with a BMI of 34 kg/m^2, along with increased physical activity, resulted in a 58% reduction in the incidence of diabetes (23).

In response to the increase in obesity, pharmaceutical

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treatments for obesity have become both more numerous and more commonly used. Drugs prescribed for weight loss can be divided into 2 categories—appetite suppressants and lipase inhibitors—on the basis of their putative mechanisms of action. Appetite suppressants can be further subdivided on the basis of the neurotransmitters they are believed to affect. This article, which reviews the available evidence on medications used as obesity treatment in adults (**Table 1**), is part of a larger evidence report prepared for the Agency for Healthcare Research and Quality titled "Pharmacological and Surgical Treatment of Obesity." The larger report is available at www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1a.chapter.19289.

Context

The effectiveness of pharmacologic therapy in the treatment of obesity is unclear.

Contribution

This review of 79 clinical trials involving diet plus the obesity drugs sibutramine, orlistat, fluoxetine, sertraline, bupropion, topiramate, or zonisamide shows that these medications can lead to modest weight reductions of approximately 5 kg or less at 1 year. Available evidence is lacking on the effect of these drugs on long-term weight loss, health outcomes such as cardiovascular events and diabetes, and adverse effects.

Implications

Those considering pharmacologic treatment for obesity should understand that these drugs can lead to modest weight loss at 1 year, but data on long-term effectiveness and safety are lacking.

–The Editors

METHODS

Literature Search and Selection

Our search for controlled human studies of pharmacologic treatments of obesity began with an electronic search of MEDLINE on 16 October 2002. Subsequently, our librarian conducted "current awareness" search updates on 22 May, 2 June, 12 June, and 3 July 2003. We also searched the Cochrane Controlled Clinical Trials Register Database and existing systematic reviews. Full details of the search strategy are available in the larger evidence report.

To be accepted for analysis, a study of drug therapy had to be a controlled clinical trial that assessed the effect of one of the pharmaceutical agents in humans and reported at least 6-month weight loss outcomes in pounds or kilograms. We made an exception for topiramate, for which most trials reported only percentage of weight loss. Patients in included studies needed to have a BMI of 27 kg/m^2 or greater.

The technical expert panel for our evidence report determined which pharmaceutical agents would be included. The panel chose sibutramine, orlistat, phentermine, and diethylpropion, all of which have been approved by the U.S. Food and Drug Administration, as well as other medications being used for weight loss, including fluoxetine, bupropion, sertraline, topiramate, and zonisamide.

Extraction of Study-Level Variables and Results

Three reviewers, working in groups of 2, extracted data from the same articles and resolved disagreements by consensus. A senior physician resolved any remaining disagreements. We used the Jadad score to evaluate the quality of the studies, using information on study design, method of random assignment, blinding, and withdrawal (34). Jadad scores range from 0 (lowest quality) to 5 (highest quality). We also collected information on withdrawal and dropout rates and calculated the percentage of attrition by dividing the number of patients providing follow-up data by the number of patients initially enrolled.

Of the medications we assessed, 3 had up-to-date existing meta-analyses (sibutramine, phentermine, and diethylpropion) and 4 others had a sufficient number of new studies to justify a new meta-analysis (orlistat, fluoxetine, bupropion, and topiramate). However, because heterogeneity was too great for the fluoxetine studies, they are summarized narratively.

Selection of Trials for Meta-Analysis

The outcome of interest was weight loss between baseline and follow-up. To make our analyses comparable, we stratified them in the same manner as did the recent meta-analysis on sibutramine (35). We defined data collected at 6 months to be data collected at any point between 16 and 24 weeks; likewise, 1-year follow-up data were those collected at any point between 44 and 54 weeks. If a study presented data for 2 or more time points in an interval, for example, 16 and 18 weeks, we chose the longest follow-up measurement for our analysis.

Mean Difference

For each trial, we extracted the follow-up mean weight loss for the control group, the follow-up mean weight loss for the medication group, and the standard deviation for each group. We then calculated a mean difference for each study, which was the difference between follow-up mean weight loss in the control group versus the medication group.

Sensitivity Analyses

We conducted sensitivity analyses on 4 study dimensions: Jadad quality score ($\leq$2 vs. $\geq$3), year of publication (1998 or earlier vs. 1999 or later), completion rate ($<$80% vs. $\geq$80% and $<$70% vs. $\geq$70%), and dosage. We tested for differences between subgroups (for example, high-quality vs. lower-quality studies) by conducting a meta-regression analysis using a single dichotomous variable to indicate subgroup membership. We conducted sensitivity analyses to determine the possible impact of dropouts. In

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Table 1. **Prescription Medications Used for Weight Loss***

Medication	Description
Appetite suppressants	
Sibutramine	A combined norepinephrine and serotonin reuptake inhibitor. Its putative effect on weight loss is attributed to appetite suppression and increased thermogenesis, secondary to stimulation of brown adipose tissue. Sibutramine was approved in 1998 for use in conjunction with a low-calorie diet as an aid to weight loss (25). Average wholesale price for 1 month of sibutramine, 10 mg/d: $103.80 USD
Fluoxetine	An SSRI that was originally approved to treat depression. The original manufacturer submitted a New Drug Application for use of fluoxetine as a weight loss drug in the early 1990s; however, the application was eventually withdrawn (Croghan T. Personal communication). Average wholesale price for 1 month of fluoxetine, 20 mg/d: $79.94 USD
Sertraline	Like fluoxetine, an SSRI. In the early 1990s, it was noted that sertraline administered to laboratory animals resulted in weight loss (26, 27). Average wholesale price for 1 month of sertraline, 200 mg/d: $86.21 USD
Phentermine	A sympathomimetic amine of the β-phenethylamine family. It was approved for use by the FDA in 1959 as a short-term aid to weight loss in conjunction with a low-calorie diet and exercise. Unlike sibutramine, phentermine leads to the development of tolerance (28). Average wholesale price for 1 month of phentermine, 30 mg/d: $39.59 USD
Diethylpropion	Like phentermine, a sympathomimetic agent prescribed for short-term weight loss when used in conjunction with diet and exercise. Diethylpropion is similar in chemical structure to bupropion, which is approved as an antidepressant and as a smoking cessation aid and has also been tested as a weight loss aid (29). Average wholesale price for 1 month of diethylpropion, 75 mg/d: $40.73 USD
Zonisamide	Approved by the FDA in 2000 for the treatment of partial (focal) seizures in adults with epilepsy, in conjunction with other anticonvulsant agents. Although the precise mechanism of action is unknown, it may exert its effects by acting as a sodium- or calcium-channel blocker. Because one of zonisamide's side effects is appetite suppression, its use as a weight loss drug has been tested (30). Average wholesale price for 1 month of zonisamide, 600 mg/d: $414.05 USD
Topiramate	An anticonvulsant agent approved in the mid-1990s for the treatment of refractory seizures in conjunction with other anticonvulsant agents. In the process of testing topiramate for treatment of mood disorders, it was discovered that the agent might mitigate the weight gain often observed with antidepressant treatment (31), and a dose-ranging study established that it does so in a dose-dependent manner (24, 32). Average wholesale price for 1 month of topiramate, 200 mg/d: $159.84 USD
Lipase inhibitors	
Orlistat	Orlistat was approved in the late 1990s and is currently the only lipase inhibitor approved for weight loss. Lipase inhibitors putatively aid weight loss by reversibly binding to the active center of the enzyme lipase, preventing the digestion and absorption of some dietary fats. Orlistat inhibits approximately 30% of fat absorption, including the absorption of fat-soluble vitamins (33). Average wholesale price for 1 month of orlistat, 360 mg/d: $170.64 USD

* Numbers in parentheses are references. FDA = U.S. Food and Drug Administration; SSRI = selective serotonin reuptake inhibitor; USD = U.S. dollars.

these analyses, we assumed that all patients who dropped out had a weight loss of zero. The mean weight loss for a particular study was then recalculated on the basis of the complete sample of both responders and dropouts. We assumed that the standard deviation of weight loss for a study did not change and recalculated the standard error on the basis of the complete sample size. We then conducted a pooled analysis for each medication and follow-up time as performed in the original approach.

Meta-Analysis of Weight Loss

For the 6-month and 12-month analyses, we estimated a pooled DerSimonian–Laird random-effects estimate (36) of the overall mean difference. The mean differences in the individual trials are weighted by both within-study variation and between-study variation in this synthesis. We also report *P* values derived from the chi-square test of heterogeneity based on the Cochran Q-test (37), and the I^2 statistic (38). This latter statistic represents the percentage of study variability that is due to heterogeneity rather than chance and is independent of the number of studies and the effect size metric.

Publication Bias

We assessed the possibility of publication bias by evaluating a funnel plot. We also conducted an adjusted rank correlation test (39) as a formal statistical test for publication bias.

Extraction of Data on Adverse Events

We assessed evidence of adverse events from randomized, controlled trials (RCTs) only. We did not include observational studies or case series data. Each trial included in the weight loss analysis was examined to determine whether it reported data on adverse events. Adverse events were recorded as the number of events or the number of people, depending on how the trial chose to report events. Most trials recorded the number of events rather than the number of unique people who experienced the event. Each event was counted as if it represented a unique individual. Because a single individual might have experienced more than 1 event, this assumption may have overestimated the number of people who had an adverse event.

Meta-Analysis of Adverse Events

For subgroups of events that occurred in 2 or more trials, at least once in the medication group and at least once in the control group, we performed a meta-analysis to estimate the pooled odds ratio and its associated 95% CI. Given that many of the events were rare, we used exact conditional inference to perform the pooling rather than applying the usual asymptotic methods that assume normality.

For interpretability, for any significant pooled odds ratio greater than 1 (which indicates that the odds of the adverse event being associated with medication is larger than the odds of it being associated with the control group), we calculated the relative risk. To perform these

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calculations, we assumed that the expected rate of the adverse event in an untreated population was equal to the observed crude rate among all controls.

We also constructed a 1-sided exact binomial 95% CI to determine the highest adverse event rate among patients receiving medication that was consistent with the zero adverse events observed among the total number of medication-treated patients in the included medication trials. We report the upper bound of this confidence interval.

Statistical Analysis

Except for the adverse events meta-analysis, we conducted all analyses and drew all graphs using Stata (Stata Corp., College Station, Texas). We conducted the adverse events meta-analysis using the statistical software package StatXact (Cytel Software Corp., Cambridge, Massachusetts).

Role of the Funding Source

The funding source had no role in the design or execution of the study or in reporting the results.

RESULTS

Results of the Literature Search

Our search identified 1103 articles (**Figure 1**). Of the 1064 articles screened, we identified up-to-date meta-analyses of sibutramine, phentermine, and diethylpropion and assessed 78 medication studies that reported on sertraline (1 article), zonisamide (1 article), orlistat (50 articles), bupropion (5 articles), topiramate (9 articles), and fluoxetine (13 articles). We found only 1 direct comparison of weight loss medications. Consequently, our results focused on the efficacy of medications relative to placebo. Full evidence tables of all studies assessed may be accessed at www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1a.section.19662.

Efficacy of Medications

Sibutramine

Our literature search identified a high-quality meta-analysis that was in press at the time of our search and has since been published (35). Included studies were RCTs that assessed sibutramine (10 mg/d to 20 mg/d), enrolled adults 18 years of age or older who had a BMI of 25 kg/m^2 or more, assessed weight loss, and had a treatment duration of at least 8 weeks. The primary outcome was mean change in body weight. Data on blood pressure; heart rate; and levels of cholesterol, fasting glucose, and glycosylated hemoglobin were abstracted if reported. Studies were analyzed in 3 strata based on trial duration: 8 to 12 weeks, 16 to 24 weeks, and 44 to 54 weeks. Of 1245 potentially relevant citations, 432 manuscripts and abstracts were reviewed in more detail, which resulted in 44 trials that were considered for inclusion in the analysis. Ten authors provided additional unpublished data. The mean age of enrolled patients ranged from 34 to 54 years. Adults with known cardiovascular disease were generally excluded from most primary studies. Dietary interventions were a co-intervention in nearly all primary studies, and exercise and behavior modification were each interventions in about one quarter of the studies. Ultimately, 29 studies met all of the authors' inclusion criteria. Of these, 23 (79%) had a Jadad score of 3 or greater.

Among the 12 trials reporting results at 16 to 24 weeks, the authors reported weight loss varying from 3.4 to 6.0 kg compared with placebo, depending on how the study was conducted. The authors detected statistical evidence of publication bias in these trials. Among the 5 studies that assessed outcomes at 44 to 54 weeks' duration, the summary mean difference in weight loss was 4.45 kg, favoring sibutramine (**Figure 2**) ($P = 0.14$ [chi-square test of heterogeneity]; $I^2 = 43\%$). This result was changed little by the authors' sensitivity analysis, and no evidence of publication bias was detected.

Regarding other assessed outcomes, the authors did not identify any evidence that sibutramine reduces mortality or morbidity from obesity-associated diseases. Systolic and diastolic blood pressure outcomes varied; some studies reported small decreases, and other studies reported small increases. Fasting blood glucose level and hemoglobin A_{1c} level decreased slightly in sibutramine-treated patients, but no consistent effect on cholesterol or lipid outcomes was observed. Analysis of adverse events identified no studies in which participants died. The analysis showed that in patients who took sibutramine, heart rate was consistently increased by about 4 beats/min.

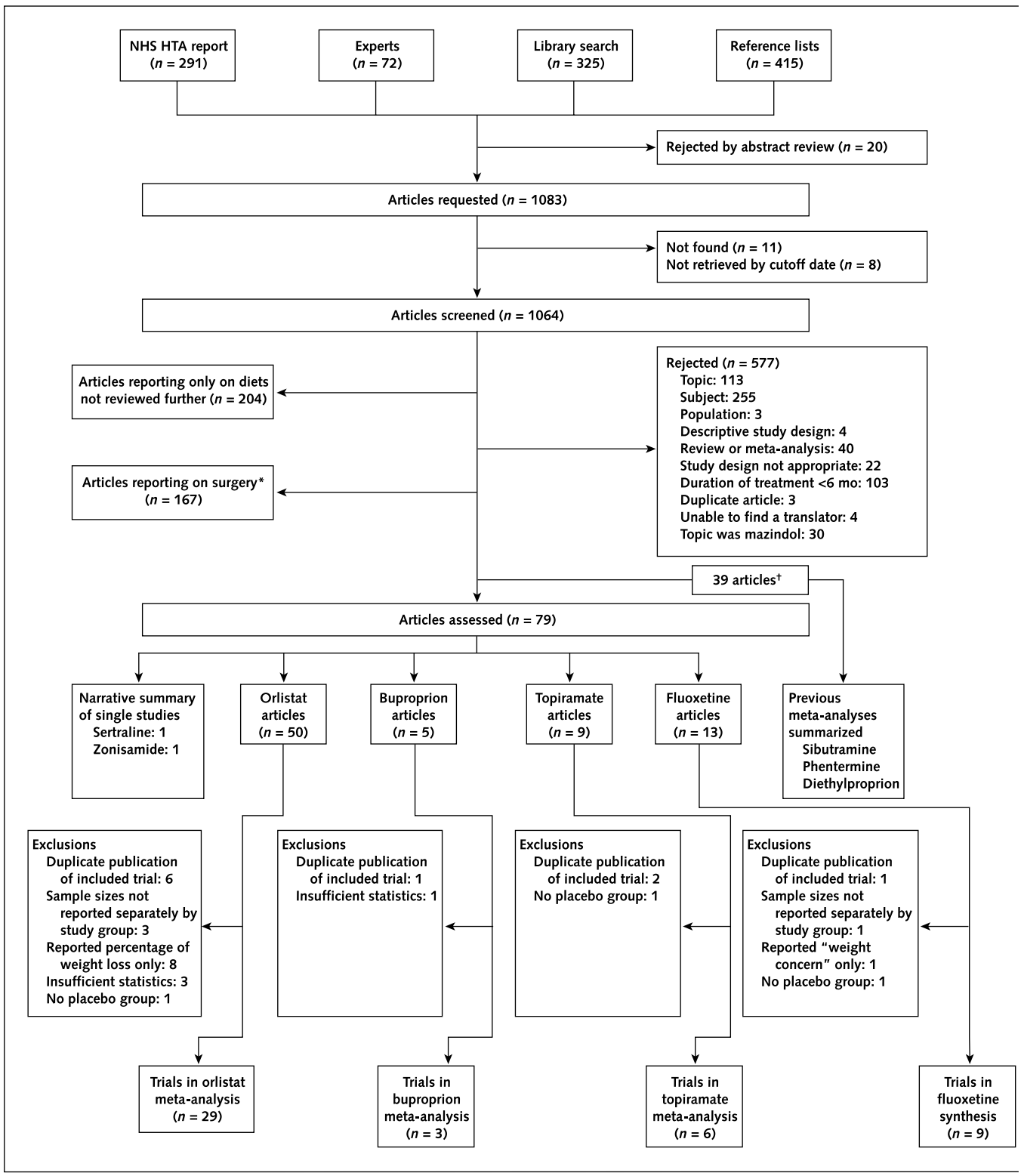
This systematic review and meta-analysis concluded that sibutramine with lifestyle modification was more effective than placebo with lifestyle modification in promoting weight loss in overweight and obese adults at all time points assessed. An average of 4.5 kg more weight was lost at 1 year in the sibutramine group, and patients taking sibutramine had a 20% to 30% greater likelihood of losing at least 5% of their body weight than did patients receiving placebos. The authors also concluded that treatment with sibutramine is associated with modest increases in heart rate and blood pressure, very small improvements in glycemic control among diabetic persons, and (based on the longest and best-quality studies) small improvements in high-density lipoprotein cholesterol and triglyceride levels. Efficacy and safety beyond 2 years of treatment are unknown. Although no serious adverse events were reported in the RCTs of sibutramine, the upper limit of the 1-sided 95% CI given the number of patients studied who received sibutramine was 0.15%, meaning that the rate of serious adverse events could be as high as 1.5 per 1000.

Orlistat

Our literature search identified 29 studies of orlistat that were eligible for inclusion in a meta-analysis (45–73). The average age of patients enrolled in these studies was 48

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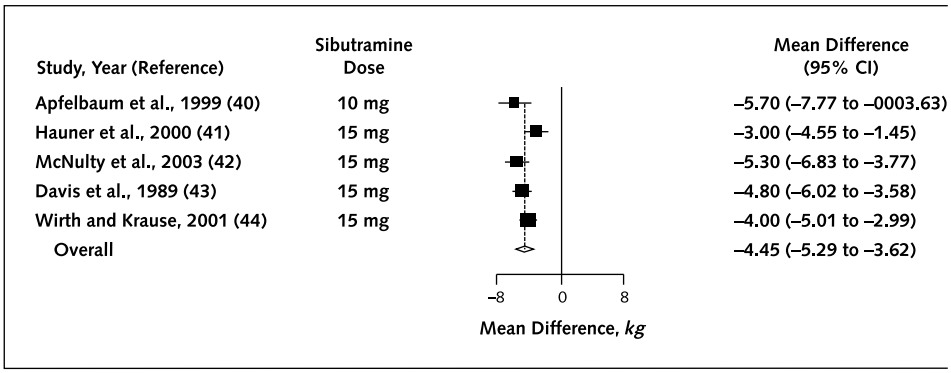
Figure 1. **Literature flow.**



HTA = Health Technology Assessment; NHS = National Health Service. *See the companion article by Maggard et al. in this issue. †These 39 articles were randomized, controlled trials and reviews of sibutramine, phentermine, and diethylpropion.

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Figure 2. **Pooled analysis of weighted mean difference in weight loss with sibutramine versus placebo at 44 to 54 weeks.**



Data are from reference 35. $P = 0.14$ (chi-square test); $I^2 = 43\%$.

years. Seventy-three percent were women, and the average BMI was 36.7 kg/m^2. In all 29 studies, diet was a co-intervention in all experimental arms. Thirty-nine percent of studies included educational, behavioral, or psychosocial co-interventions, and 18% of studies included exercise co-interventions. Consistent with the meta-analysis of sibutramine, we stratified the data according to treatment duration for analysis.

We identified 12 studies (45, 51, 53–55, 57, 59, 65, 68, 69, 72, 73) that reported 6-month treatment outcomes. The pooled random-effects estimate of the mean weight loss for orlistat-treated patients compared with placebo recipients was 2.59 kg (95% CI, 1.74 to 3.46 kg). The total weight lost in the orlistat-treated patients was 5.39 kg. Significant heterogeneity was found among studies ($I^2 = 86\%$; $P < 0.01$). Sensitivity analyses by study quality, year of publication, dose, and attrition rate did not yield different results. A sensitivity analysis assuming no weight loss among patients lost to follow-up yielded a mean weight loss favoring orlistat of 2.54 kg (CI, 1.56 to 3.52 kg). No evidence of publication bias was found.

We identified 22 studies (45–51, 56–58, 60–64, 66, 67, 69–73) that reported data with 12-month outcomes. The weight loss for individual studies is presented in **Figure 3**. The pooled random-effects estimate of the mean weight loss for orlistat-treated patients compared with placebo recipients was 2.89 kg (CI, 2.27 to 3.51 kg). The total weight lost in the orlistat-treated patients was 8.13 kg. Significant heterogeneity was observed among studies ($I^2 = 83\%$; $P < 0.001$). In a sensitivity analysis by study quality, 15 studies with a Jadad score of 3 or more had a pooled random-effects estimate of mean weight loss of 2.58 kg (CI, 1.9 to 3.3 kg). No effect of quality score on outcome was detected by meta-regression, and no effect of year of publication on outcome was detected. Sensitivity analysis by dose was not possible. In a sensitivity analysis by follow-up rate, the pooled random-effects estimate of 15 studies with follow-up rates of 70% or more was a mean weight loss of 2.83 kg (CI, 2.0 to 3.6 kg) compared with placebo; when 80% was used as the threshold for successful follow-up, no effect of completeness of follow-up on outcome was detected by meta-regression. A sensitivity analysis assuming no weight loss among patients lost to follow-up yielded a mean weight loss favoring orlistat of 2.59 kg (CI, 1.90 to 3.29 kg). There was no evidence of publication bias.

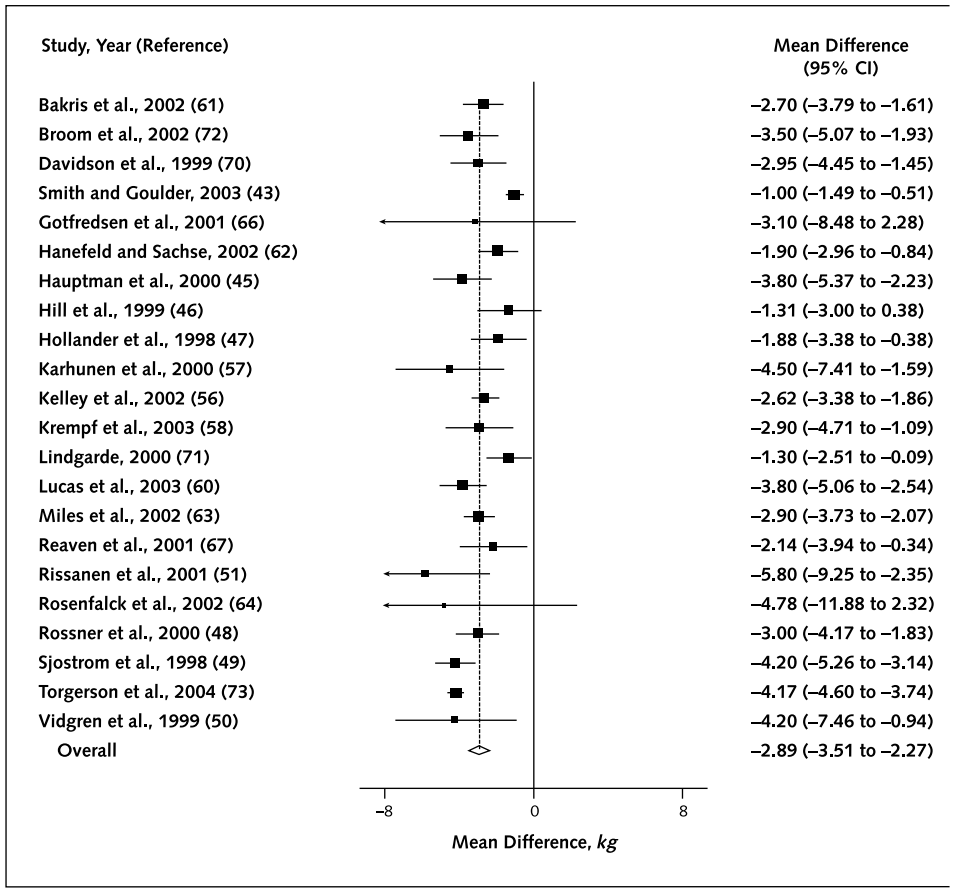
In our adverse event analysis, all 29 studies were considered for inclusion. Our results indicate an increase in diarrhea (relative risk, 3.40); flatulence (relative risk, 3.10); and bloating, abdominal pain, and dyspepsia (relative risk, 1.48) in orlistat-treated patients compared with placebo. Five trials reported more incidents of diarrhea than the number of enrolled patients; for these 5 trials (out of 13 trials reporting this complication), we assumed all patients reported this event. Therefore, we may have overestimated the true risk for diarrhea. Nevertheless, our data suggest that orlistat causes clinically significant gastrointestinal side effects. We attempted to determine whether the proportion of persons reporting adverse events decreased over time, but since our search strategy eliminated studies with a duration of less than 6 months, we could assess only whether adverse event reports differed between 6 and 12 months. No difference was detected. Although no serious adverse events were reported in the RCTs of orlistat, the upper limit of the 1-sided 95% CI given the number of patients studied who received orlistat was 0.03%, meaning that the rate of serious adverse events could be as high as 3 per 10 000.

Phentermine

Our literature search identified a recent meta-analysis (74) that assessed RCTs of the use of phentermine for weight loss in obese individuals. This review identified 9 studies published between 1975 and 1999. Our literature review identified no new RCTs of phentermine since this time. In the previously published review, 6 placebo-controlled RCTs contributed data to the pooled analysis. The duration of treatment with phentermine varied from 2 to 24 weeks. More than 80% of enrolled individuals were

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Figure 3. **Pooled analysis of mean difference in weight loss with orlistat versus placebo at 12 months.**



$P = 0.00$ (chi-square test); $I^2 = 83\%$.

women, and more than 80% of participants also received lifestyle modification treatments as co-interventions. The dosage of phentermine ranged from 15 mg/d to 30 mg/d. In the authors' pooled analysis, patients treated with phentermine lost an average of 3.6 kg (CI, 0.6 to 6.0 kg) of additional weight compared with placebo. The authors concluded that phentermine use, in addition to lifestyle interventions, resulted in a statistically significant but modest increase in weight loss. In this review, no data on side effects or adverse events were reported. We identified no systematic reports of adverse events with phentermine. However, since phentermine is a sympathomimetic amine, side effects consistent with this class of drugs can be expected, for example, palpitations, tachycardia, elevation of blood pressure, central nervous system effects, and gastrointestinal effects. There have been case reports of stroke in persons taking phentermine for weight loss (75, 76), but as with all case report analyses, a causal relationship cannot be established or assumed. Although no serious adverse events were reported in the RCTs of phentermine, the upper limit of the 1-sided 95% CI given the number of patients studied who received phentermine was 1.5%, meaning that the rate of serious adverse events could be as high as 15 per 1000.

Diethylpropion

Our literature search identified a recent meta-analysis (74) that assessed RCTs of the use of diethylpropion for weight loss in obese individuals. This review identified 13 studies published between 1965 and 1983. Our literature review identified no new RCTs of diethylpropion since this time. In the previously published review, 9 placebo-controlled RCTs contributed data to the pooled analysis. The duration of treatment with diethylpropion varied from 6 to 52 weeks. More than 80% of enrolled individuals were women, and 100% of participants received lifestyle modification treatments as co-interventions. The dosage of diethylpropion was 75 mg/d. In the authors' pooled analysis, patients treated with diethylpropion lost an average of 3.0 kg (CI, −1.6 to 11.5 kg) of additional weight compared with placebo. The authors concluded that diethylpropion use, in combination with lifestyle interventions, was associated with a modest increase in weight loss of borderline statistical significance. In this review, no data on side effects or adverse events were reported. According to standard references, the pharmacologic effect of diethylpropion is similar to that of amphetamines, and common side effects include central nervous system stimulation, dizziness, headache, insomnia, restlessness, mild increases in blood

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pressure, palpitations, mild tachycardia, mild gastrointestinal symptoms, and rash (77). Although no serious adverse events were reported in the RCTs of diethylpropion, the upper limit of the 1-sided 95% CI given the number of patients studied who received diethylpropion was 1.5%, meaning that the rate of serious adverse events could be as high as 15 per 1000.

Fluoxetine

Our literature search identified 9 studies of fluoxetine treatment that reported weight loss outcomes (fluoxetine is normally prescribed for treatment of depression, obsessive–compulsive disorder, and bulimia) (78–86). Of note, doses used for weight loss were higher (60 mg) than those used for depression (20 mg). The average age of patients enrolled in these studies was 48 years. Sixty-nine percent were women, and the average BMI was 35.5 kg/m^2. In 78% of the studies (7 of 9), diet was a co-intervention; 33% included an educational, behavioral, or psychosocial co-intervention; and 12% included exercise as a co-intervention. The statistical tests and Forest plot of individual study results revealed too much heterogeneity, so pooled analyses are not presented.

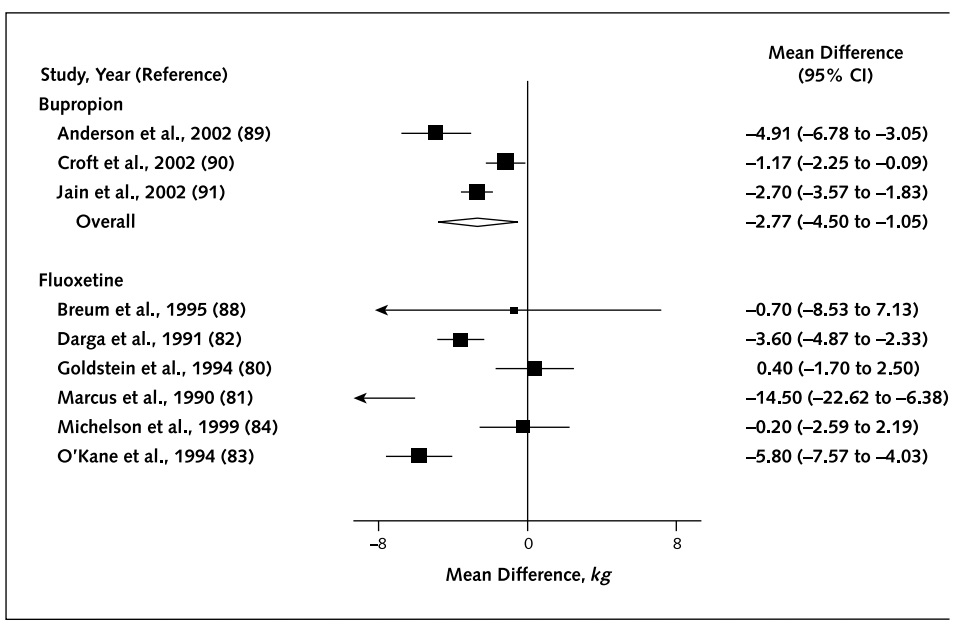
We identified 7 studies of fluoxetine that reported weight loss outcomes at 6 months (78, 79, 81, 83–86). Six of the 7 reported statistically significant weight loss in fluoxetine-treated patients. Weight loss relative to placebo in all 7 studies ranged from 0.90 kg to 9.1 kg. We identified 6 studies of fluoxetine that reported weight loss outcomes at 12 months (78–82, 86). The individual results for studies are shown in **Figure 4**. In contrast to the studies reporting 6-month outcomes, only half of these studies reported statistically significant weight loss in fluoxetine-treated patients. Weight loss relative to placebo ranged from 14.5 kg lost to 0.4 kg gained. Year of publication, quality scores, and dose did not affect the results. In an analysis based on follow-up rate or assuming no weight loss among patients lost to follow-up, a noticeable trend toward less weight lost was observed. We did not detect any evidence of publication bias.

In the adverse event analysis, which included all 9 studies, fluoxetine-treated patients experienced increased nervousness, sweating, and tremors (relative risk, 6.37); nausea and vomiting (relative risk, 2.68); fatigue, asthenia, hypersomnia, and somnolence (relative risk, 2.36); insomnia (relative risk, 2.06); and diarrhea (relative risk, 1.74) compared with placebo recipients. The literature on the use of fluoxetine for other indications is extensive, and the results of our analysis are compatible with the adverse events reported in those studies.

Sertraline

Our literature search identified 1 study of sertraline (90). This study assessed the effect of sertraline in maintaining weight loss in 53 of 68 women who had completed a 26-week weight reduction program that combined a very-low-calorie diet and behavior therapy. At the end of the 54-week evaluation, sertraline-treated patients had regained an average of 17.7 kg, while placebo recipients had regained an average of 11.8 kg, a difference the authors did not report as statistically significant.

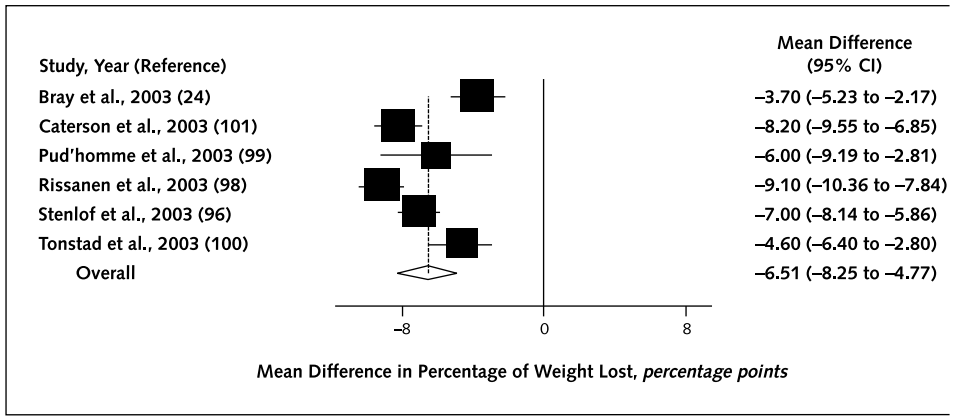
Figure 4. **Pooled analysis of weight loss with bupropion and fluoxetine versus placebo at 6 to 12 months.**



For bupropion, $P = 0.00$ (chi-square test) and $I^2 = 84\%$. For fluoxetine, $P = 0.00$ (chi-square test) and $I^2 = 85\%$.

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Figure 5. **Pooled analysis of weight loss with topiramate versus placebo at 6 months.**



$P = 0.00$ (chi-square test) and $I^2 = 87\%$.

Bupropion

Our literature search identified 5 articles assessing the efficacy of bupropion for weight loss. Of the 5, 1 article (91) was an abstract that reported the same data as did a subsequent full report (87), so only 4 articles reported on unique studies. One of those studies was dropped because the duration of treatment and follow-up was only 8 weeks, which left 3 studies available for a pooled analysis. In these 3 studies, the average age of enrolled patients was 43 years. Eighty-one percent were women, and the average weight was 94.3 kg. Patients in 1 study (88) had major depression, and those in another (89) had depressive symptoms. Two studies reported results at 6 months (87, 89), and 1 study reported results at 12 months (88). Therefore, we could not perform separate analyses by time point, and readers should keep in mind that our pooled result for bupropion is a mix of 6- and 12-month outcomes. Two of the 3 studies included diet as a co-intervention, and 1 study included exercise. One study reported results for 300 mg and 400 mg of bupropion per day; the other 2 studies assessed only the 400 mg/d dosage. In this analysis, we present results only for 400 mg of bupropion per day compared with placebo.

The individual weight loss values for each study are shown in **Figure 4**. The pooled random-effects estimate of the weight loss in bupropion-treated patients compared with placebo recipients was 2.77 kg (CI, 1.1 to 4.5 kg). The total weight loss in the bupropion-treated patients was 4.44 kg. There was significant heterogeneity among studies ($I^2 = 84\%$; $P < 0.001$). The pooled results need to be considered in light of the individual study results. All 3 individual studies and the pooled results report statistically significant weight loss, but the magnitude varies substantially. There were too few studies to support sensitivity analyses based on study quality, year of publication, or dose. A sensitivity analysis assuming no weight loss among patients lost to follow-up yielded a mean weight loss of 2.66 kg (CI, 1.0 to 4.33 kg) favoring bupropion. We did not detect any evidence of publication bias.

In the adverse event analysis, there was an increase in dry mouth (pooled odds ratio, 3.26; relative risk, 2.99) and nonsignificant increases in diarrhea and constipation. The research literature on the use of bupropion for depression and smoking cessation is extensive. In addition to dry mouth, insomnia is a commonly reported side effect in these studies.

Topiramate

Our literature search identified 9 studies that assessed the efficacy of the drug topiramate for weight loss. One study (92), which did not include a placebo group, was excluded from review, and another study (93) was dropped because it duplicated data in another included study (24). Two articles reported data on the same trial (94, 95); however, we included only the study with the larger sample size, leaving 6 studies for analysis (24, 95–99). All but 1 of these studies were published only as abstracts at the time of our analysis. Of note, all of these studies reported their data only as percentage of weight loss, so the outcome for this analysis was percentage of weight loss. Many of the studies assessed multiple dosages, the most common being 96 mg/d and 192 mg/d. We determined that the higher dosage produced significantly more weight loss than the lower dosage (a 1.75% absolute increase) over the duration of the study, so we present data only on the higher dose. In these studies, the average age of patients was 47 years. Sixty-eight percent were women, and the baseline weight was 102 kg. Four of the 6 studies used diet, exercise, education, and behavioral therapies as co-interventions.

The individual percentage weight loss values for the 6 studies reporting 6-month weight loss outcomes are shown in **Figure 5**. The pooled random-effects estimate of the percentage of weight loss in topiramate-treated patients compared with placebo recipients was 6.5% (CI, 4.8% to 8.3%) ($I^2 = 87\%$; $P < 0.001$ for heterogeneity). The total percentage of weight lost in the topiramate-treated patients was 8%, and there was significant heterogeneity among

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studies. The pooled result needs to be considered in light of the individual study results. All 6 individual studies and the pooled result report statistically significant weight loss, but the magnitude varies substantially. In a sensitivity analysis of study quality, only 1 study had a Jadad score of 3 or greater (because studies were assessed on the basis of data in abstracts, this finding may have been the result of the incomplete nature of the report), and its exclusion did not materially alter the pooled result. All studies were recent, so no sensitivity analysis by year of publication could be performed. Only 1 study reported a follow-up rate of less than 80%, and its exclusion did not materially alter the pooled result. A sensitivity analysis assuming no weight loss among patients lost to follow-up yielded a mean weight loss favoring topiramate of 3.6% (CI, 2.6% to 4.8%). We did not detect any evidence of publication bias.

In the adverse event analysis, paresthesia and changes in taste were reported much more commonly in topiramate-treated patients than in placebo recipients (pooled odds ratios, 20.18 and 11.14, respectively; relative risk, 4.92 and 9.19, respectively). Other central nervous system effects and gastrointestinal effects were also reported more commonly in topiramate-treated patients. Adverse events were more common in patients treated with 192 mg of topiramate per day than in those treated with 96 mg/d. Although no serious adverse events were reported in the RCTs of topiramate, the upper limit of the 1-sided 95% CI given the number of patients studied who received topiramate was 0.6%, meaning that the rate of serious adverse events could be as high as 6 per 1000.

Zonisamide

Our literature search identified 1 eligible study that assessed the efficacy of the drug zonisamide for weight loss in a 32-week study (100). This study was a double-blind RCT that enrolled 60 patients with a mean age of 37 years, of whom 92% were women. Mean BMI was 36 kg/m^2. Patients were randomly assigned to begin receiving placebo or zonisamide at 100 mg/d; daily doses were increased to a maximum of 600 mg on the basis of response. The authors reported that at the end of the 16-week double-blind portion of the study, patients in the zonisamide group lost an average of 6.0% of baseline body weight, compared with 1.0% for placebo recipients ($P < 0.001$).

Summary of Medication Studies

Tables 2, **3**, and **4** briefly summarize our findings regarding medications. As previously stated, we identified only 1 study that directly compared weight loss medications (101). This study assessed 150 women who were randomly assigned to receive sibutramine, orlistat, or metformin. At 6 months, all 3 groups reported statistically and clinically significant weight loss of about 8 to 13 kg. The sibutramine-treated group lost about 4 to 5 kg more than the other groups, a difference the authors reported as statistically significant (but insufficient data were included with the article to verify this). Our summary of the results for each drug (compared with placebo) does not support a hypothesis that any one drug is more effective than the others, since the difference among drugs in placebo-corrected mean weight loss at 1 year is only about 1 to 2

Table 2. **Summary of Findings on Medications for Weight Loss***

Medication	Source of Data	Characteristics of Study Patients	Period at Which Weight Loss Was Assessed, *wk*	Mean Weight Change in Treated Patients Compared with Placebo (95% CI)
Sibutramine	Existing meta-analysis of 29 RCTs	Mean age, 34–54 y; 53% to 100% women; average BMI not reported	52	−4.45 kg (−5.29 to −3.62 kg)
Orlistat	The authors' meta-analysis of 22 RCTs	Average age, 48 y; 73% women; average BMI, 36.7 kg/m^2	52	−2.75 kg (−3.31 to −2.20 kg)
Fluoxetine	Narrative synthesis of 9 RCTs	Average age, 48 y; 69% women; average BMI, 35.5 kg/m^2	52	Range in weight loss varied among studies from 14.5 kg lost to 0.4 kg gained
Sertraline	1 RCT	Average age, 42 y; 100% women; average BMI, 30 kg/m^2	26	In maintenance trial, no significant difference between drug and placebo
Phentermine	Existing meta-analysis of 9 RCTs	Average age, NA; 78% women; average BMI, NA	2 to 24	−3.6 kg (−6.0 to −0.6 kg)
Diethylpropion	Existing meta-analysis of 13 RCTs	Average age, NA; 80% women; average BMI, NA	6 to 52	−3.0 kg (−11.5 to 1.6)
Bupropion	The authors' meta-analysis of 3 RCTs	Average age, 43 y; 81% women; average weight, 94.3 kg	24 to 52	−2.77 kg (−4.5 to −1.0 kg)
Topiramate	The authors' meta-analysis of 6 RCTs	Average age, 47 y; 68% women; average weight, 102 kg	24	Additional 6.5% (CI, 4.8% to 8.3%) of pretreatment weight lost
Zonisamide	1 RCT	Mean age, 37 y; 92% women; average BMI, 36 kg/m^2	16	Additional 5% of pretreatment weight lost

* BMI = body mass index; NA = not available; RCT = randomized, controlled trial.

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Table 3. **Summary of Findings regarding Adverse Events according to Medications for Weight Loss***

Adverse Event by Drug	Pooled OR (95% CI)	Relative Risk	Number Needed To Treat for Harm†
Orlistat			
Diarrhea	54.85 (44.88–67.48)	3.40	1.48
Flatulence	3.72 (3.16–4.39)	3.10	6.49
Bloating, abdominal pain, and dyspepsia	1.55 (1.18–2.06)	1.48	25.80
Headache	1.18 (0.68–2.05)	Not calculated	Not calculated
Nausea and vomiting	0.95 (0.46–1.98)	Not calculated	Not calculated
Gallbladder problems	0.71 (0.27–1.82)	Not calculated	Not calculated
Depression and mood change	0.33 (0.01–4.15)	Not calculated	Not calculated
Fluoxetine			
Nervousness, sweating, and tremors	7.85 (3.87–17.63)	6.37	5.48
Nausea and vomiting	3.27 (1.94–5.67)	2.68	6.17
Fatigue, asthenia, hypersomnia, and somnolence	2.83 (1.82–4.45)	2.36	6.70
Insomnia	2.19 (1.10–4.58)	2.06	18.15
Diarrhea	1.86 (1.10–3.23)	1.74	17.37
Urticaria, pruritus, and rash	1.67 (0.53–5.65)	Not calculated	Not calculated
Headache	1.35 (0.91–2.03)	Not calculated	Not calculated
Rhinitis	1.08 (0.73–1.60)	Not calculated	Not calculated
Bupropion			
Dry mouth	3.26 (1.71–6.64)	2.99	12.43
Diarrhea	1.37 (0.52–4.01)	1.34	47.19
Constipation	1.31 (0.72–2.44)	1.29	56.28
Upper respiratory problems	1.22 (0.88–1.69)	1.14	22.23
Headaches	0.99 (0.63–1.57)	Not calculated	Not calculated
Central nervous system effects	0.98 (0.58–1.66)	Not calculated	Not calculated
Upper abdominal symptoms	0.81 (0.44–1.50)	Not calculated	Not calculated
Topiramate			
Paresthesia	20.18 (13.99–29.67)	4.92	1.58
Taste perversion	11.14 (5.80–23.57)	9.19	5.85
Central nervous system effects	3.97 (2.90–5.49)	2.06	3.02
Constipation	3.96 (1.77–9.77)	3.52	9.36
Dry mouth	3.13 (1.59–6.55)	2.90	14.13
Upper abdominal symptoms	1.76 (1.27–2.47)	1.61	13.26
Fatigue	1.36 (1.03–1.80)	1.25	15.91
Upper respiratory problems	1.32 (0.87–1.99)	1.18	14.90
Diarrhea	1.08 (0.68–1.71)	1.07	89.42

* OR = odds ratio.
† OR < 1.0.

kg. In addition, none of these medications appear to support large weight loss: The mean placebo-corrected weight loss for all drugs was less than 5 kg at 1 year. Total weight loss at 1 year was higher, up to 8.0 kg. However, as noted earlier, even moderate weight loss (5% of body weight) can significantly influence obesity-associated risk factors for poor health outcome (type 2 diabetes, hypertension, and others). The side effect profiles varied substantially among medications.

Table 4. **Summary of Side Effects of Sibutramine Used for Weight Loss**

Variable	Range of Reported Mean Differences	
	Treatment Duration, 16–24 wk	Treatment Duration, 44–54 wk
Blood pressure, *mm Hg*		
Systolic	−1.6 to 5.6	4.6
Diastolic	−0.8 to 1.7	2.8
Heart rate, *beats/min*	0.75 to 5.9	5.9

DISCUSSION

Data from RCTs are sufficient to allow us to conclude that sibutramine, orlistat, phentermine, probably diethylpropion, probably fluoxetine, bupropion, and topiramate promote weight loss for at least 6 months when given along with recommendations for diet (and possibly other behavioral and exercise interventions). The amount of extra weight loss attributable to these medications is modest (<5 kg at 1 year) but still may be clinically significant. The most well-studied medications are sibutramine and orlistat. Not only have they been studied more often, their pooled estimates of efficacy and safety reflect longer time frames than other drugs. Thus, our conclusions for these medications are stronger than for the others. One RCT supports the efficacy of zonisamide for short-term weight loss, but stronger conclusions cannot be drawn without additional studies.

All of these drugs have side effects, and side effect profiles vary by drug. Sibutramine causes modest increases in heart rate and blood pressure; gastrointestinal symptoms

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predominate in the use of orlistat; phentermine causes cardiovascular and gastrointestinal side effects; fluoxetine causes agitation and nervousness in addition to gastrointestinal side effects; bupropion causes paresthesia, insomnia, and central nervous system effects; and topiramate causes paresthesia and changes in taste. The choice of medications for weight loss probably rests on individual tolerance to the side effect profile. In general, these drugs have not been studied sufficiently to evaluate the risk for rare (<1 per 1000) side effects.

Several RCTs of weight loss medications have been conducted; nevertheless, significant unanswered questions remain regarding the medications assessed in this review. One question is their long-term effect on health outcomes. With one exception, we identified no studies that assessed the effects of long-term weight loss on obesity-related health outcomes. The 1 study that assessed long-term outcomes was an RCT of orlistat or placebo plus lifestyle changes in more than 3000 obese patients (mean BMI, 37 kg/m^2), of whom 21% had impaired glucose tolerance at baseline (73). After 4 years of follow-up, weight loss was greater in the orlistat-treated patients than in placebo recipients. Likewise, the incidence of new diabetes was 37% lower in the orlistat-treated patients. Although limited by loss of follow-up (52% of the orlistat group and 34% of the placebo group completed treatment), this study supports the hypothesis that long-term treatment with orlistat can reduce weight and help prevent obesity-related health problems. Another question concerns relative efficacy and cannot be conclusively answered without more head-to-head RCTs that compare the different agents. However, the placebo-controlled trial data we reviewed suggest that if any statistically significant differences are seen, they are likely to be clinically small (a difference of a few kilograms at 12 months), although we observed a trend suggesting more weight regain at 12 months with fluoxetine than with other agents. Another relevant question regarding efficacy may be whether combinations of agents promote greater weight loss than individual agents. One study that combined orlistat and sibutramine reported no increase in weight loss over sibutramine alone (102). A fourth relevant question is whether use of any of these drugs combined with more aggressive behavioral interventions and diet therapies would be more effective than the results seen in the RCTs to date, in which many of the dietary interventions were modest. A fifth question concerns the optimal duration of treatment. We found no RCT data to answer this question; therefore, new clinical trials are needed. Some physicians believe that their overweight patients will always need to take diet medications, in essence treating overweight as a chronic disease similar to hypertension. Given that possibility, information about long-term (that is, much longer than 12 months) effectiveness and safety is needed. A recently published study has demonstrated efficacy and safety in a 4-year trial of orlistat (73). The question of side effects, particularly the possibility of rare adverse events, remains unanswered for most of these drugs.

Our literature search procedures were extensive and included canvassing experts regarding studies we may have missed. We tested for and found no evidence of publication bias. We made explicit assumptions about the lack of reporting of mortality and other adverse events and discussed the possible bias that might result. We acknowledge that publication bias may still exist despite our best efforts to conduct a comprehensive search and despite the lack of statistical evidence for the existence of bias. Another important limitation common to systematic reviews is the quality of the original studies. Most of the studies of orlistat and fluoxetine had Jadad scores of 3 or greater, a threshold that in other settings has been shown to be associated with less bias. Our sensitivity analyses on these higher-quality RCTs upheld our main result. Because empirical evidence is lacking on the relationship of other study characteristics to bias, we did not attempt to use other criteria.

Evidence of heterogeneity was observed for all of the medication meta-analyses. We used a pooled random-effects approach to attempt to incorporate any heterogeneity and assessed the results of sensitivity analyses using variables that might account for heterogeneity (quality, completeness of follow-up, dose, and year of publication). However, we could not explain most of the heterogeneity. Unexplained heterogeneity might be due to differences in study patients, setting, or study implementation. We caution the reader to interpret our pooled results in light of the observed heterogeneity by considering both the individual study results as well as the overall pooled result. Finally, the results of the studies we synthesized are directly applicable only to the persons included in those studies. In some cases, enrollment was highly selective to avoid certain comorbid conditions. Whether the results are applicable in other populations is unknown.

In summary, sibutramine, orlistat, phentermine, probably diethylpropion, bupropion, probably fluoxetine, and topiramate promote weight loss when given along with recommendations for diet. Sibutramine and orlistat are the 2 most-studied drugs. The amount of extra weight loss attributable to these medications is modest (<5 kg at 1 year), but this amount may still be clinically significant.

From the Southern California Evidence-Based Practice Center, which includes RAND Health Division, Santa Monica, and the Greater Los Angeles VA Healthcare System, Los Angeles, California; and Department of Veterans Affairs, Cincinnati, Ohio.

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Appendix Table. **Evidence Table of Randomized, Controlled Trials***

Study, Year (Reference)	Medication	Quality Score†	Population	Co-Interventions	Arm	Intervention	Patients Who Entered Study/Patients Who Completed Study, *n/n*	Mean Weight Change ± SD	Follow-up, *mo*
Anderson et al., 2002 (87)	Bupropion	3	Adult women	Hypocaloric diet, physical activity	1	Placebo	112/80	−5.2 ± 6.6 kg	6
					2	Bupropion, variable dose for 48 wk	110/67	Dropped from analysis because it used a lower dose of the same medication	
					3	Bupropion, variable dose for 48 wk	105/57	−10.1 ± 7.4 kg	
Croft et al., 2002 (88)	Bupropion	2	Adults	None	1	Placebo	213/43	0.02 ± 5.7 kg	13
					2	Bupropion, 300 mg for 44 wk	210/60	−1.2 ± 5.7 kg	
Jain et al., 2002 (89)	Bupropion	3	Adult women	Hypocaloric diet	1	Placebo	209/191	−1.7 ± 4.3 kg	6
					2	Bupropion, variable dose for 24 wk	213/195	−4.4 ± 4.4 kg	
Breum et al., 1995 (86)	Fluoxetine	3	Adults	Hypocaloric diet, cognitive–behavioral	1	Placebo	20/14	−9.4 ± 11.5 kg	12
					2	Fluoxetine, 60 mg for 52 wk	20/15	−10.1 ± 10.0 kg	
Connolly et al., 1995 (83)	Fluoxetine	3	Adults	Hypocaloric diet	1	Placebo	15/13	0.0 ± 0.5 kg	6
					2	Fluoxetine, 60 mg for 6 mo	15/11	−3.9 ± 1.5 kg	
Darga et al., 1991 (80)	Fluoxetine	3	Adults	Hypocaloric diet, education	1	Placebo	22/16	−4.6 ± 1.1 kg	12
					2	Fluoxetine, 60 mg for 52 wk	23/14	−8.2 ± 2.2 kg	
Goldstein et al., 1994 (78)	Fluoxetine	4	Adult women	Hypocaloric diet	1	Placebo	184/ND	−2.4 ± 5.4 kg	5
								−2.1 ± 6.8	12
					2	Placebo	22/ND	Collapsed into arm 1	
					3	Placebo	22/ND	Collapsed into arm 1	
					4	Fluoxetine, 60 mg for 52 wk	182/ND	−5.1 ± 6.9 kg	5
								−1.7 ± 8.7 kg	12
Gray et al., 1992 (85)	Fluoxetine	4	Adults	Hypocaloric diet	1	Placebo	24/20	−1.9 ± 2.9 kg	6
					2	Fluoxetine, 60 mg for 6 mo	24/16	−9.3 ± 2.4	
Marcus et al., 1990 (79)	Fluoxetine	4	Adult women	Hypocaloric diet, cognitive–behavioral, physical activity	1	Placebo	22/11	−2.1 ± 6.1 kg	5
								−0.7 ± 6.2 kg	9
								0.6 ± 5.0 kg	12
					2	Fluoxetine, 60 mg for 52 wk	23/13	−11.2 ± 5.8 kg	5
								−12.3 ± 9.8 kg	9
								−13.9 ± 12.7 kg	12
Mendoza Espejo et al., 1995 (84)	Fluoxetine	1	Adult women	Hypocaloric diet	1	Placebo	30/19	−7.7 ± 4.0 kg	6
					2	Fluoxetine, 180 mg for 6 mo	ND/ND	−12.3 ± 4.0 kg	
Michelson et al., 1999 (82)	Fluoxetine	1	Adults	None	1	Placebo	96/ND	1.9 ± 2.3 kg	6.5‡
								3.2 ± 4.3 kg	11.5‡
					2	Fluoxetine, 20 mg for 14 wk	97/ND	1.0 ± 2.4 kg	6.5‡
					3	Fluoxetine, 20 mg for 38 wk	100/ND	–	–
					4	Fluoxetine, 20 mg for 50 wk	102/ND	3.0 ± 4.0 kg	11.5‡

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Appendix Table—**Continued**

Study, Year (Reference)	Medication	Quality Score†	Population	Co-Interventions	Arm	Intervention	Patients Who Entered Study/Patients Who Completed Study, *n/n*	Mean Weight Change ± SD	Follow-up, *mo*
O'Kane et al., 1994 (81)	Fluoxetine	2	Adults	None	1	Placebo	10/9	0.2 ± 1.1 kg	6
								1.5 ± 1.7 kg	12
					2	Fluoxetine, 60 mg for 12 mo	10/7	−6.3 ± 0.8 kg	6
								−4.3 ± 1.9 kg	12
Bakris et al., 2002 (61)	Orlistat	3	Adults	Hypocaloric diet, education, antihypertensive medication	1	Placebo	276/108	2.7 ± 6.4 kg	12
					2	Orlistat, 360 mg for 52 wk	278/162	−5.4 ± 6.4 kg	
Broom et al., 2002 (72)	Orlistat	3	Adult women	Hypocaloric diet	1	Placebo	261/161	−2.3 ± 6.4 kg	12
					2	Orlistat, 360 mg for 52 wk	265/186	−5.8 ± 8.5 kg	
Broom, 2001 (52)	Orlistat	2	Adults	Hypocaloric diet, education	1	Placebo	71/60	−2.6 ± 3.9 kg	12
					2	Orlistat, 360 mg for 52 wk	71/34	−4.4 ± 4.1	
Davidson et al., 1999 (70)	Orlistat	3	Adult women	Hypocaloric diet, education, cognitive–behavioral, physical activity	1	Placebo	224/133	−5.8 ± 7.7 kg	12
					2	Orlistat, 360 mg for 52 wk	668/458	−8.8 ± 7.9 kg	
Deerochanawong, 2001 (54)	Orlistat	2	Adults	Hypocaloric diet, education	1	Placebo	126/ND	−1.4 ± 6.3 kg	6
					2	Orlistat, 360 mg for 24 wk	126/ND	−2.6 ± 6.3 kg	
Derosa et al., 2003 (69)	Orlistat	3	Adults	Hypocaloric diet, physical activity	1	Placebo	23/23	−4.2 ± 0.6 kg	6
								−7.6 ± 0.7 kg	12
					2	Orlistat, 360 mg for 1 y	27/25	−5.1 ± 0.7 kg	6
								−8.6 ± 1.1 kg	12
					3	Fluvastatin, dosage and duration NR	24/24	Excluded because it used different medications	
					4	Orlistat + fluvastatin, 360 mg for 1 y	25/24	Excluded because it used different medications	
Gotfredsen et al., 2001 (67)	Orlistat	3	Adult women	Hypocaloric diet	1	Placebo	14/ND	−8.1 ± 7.5 kg	12
					2	Orlistat, 360 mg for 1 y	16/ND	−11.2 ± 7.5 kg	
Halpern et al., 2003 (59)	Orlistat	4	Adults	Hypocaloric diet, cognitive–behavioral	1	Placebo	174/141	−2.58 ± 17.3 kg	6
					2	Orlistat, 360 mg for 6 mo	169/139	−4.24 ± 2.7 kg	
Hanefeld et al., 2002 (62)	Orlistat	2	Adults	Hypocaloric diet	1	Placebo	188/180	−3.4 ± 5.3 kg	12
					2	Orlistat, 360 mg for 48 wk	195/189	−5.3 ± 5.1 kg	
Hauptman et al., 2000 (45)	Orlistat	3	Adult women	Hypocaloric diet, education, cognitive–behavioral, physical activity	1	Placebo	212/91	−4.7 ± 8.7 kg	6
								−4.1 ± 8.2 kg	12
					2	Orlistat, 180 mg for 2 y	213/120	Excluded because of low dosage	
					3	Orlistat, 360 mg for 2 y	210/117	−8 ± 8.4 kg	6
								−7.9 ± 8.3 kg	12

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Appendix Table—**Continued**

Study, Year (Reference)	Medication	Quality Score†	Population	Co-Interventions	Arm	Intervention	Patients Who Entered Study/Patients Who Completed Study, *n/n*	Mean Weight Change ± SD	Follow-up, *mo*
Hill et al., 1999 (46)	Orlistat	3	Adult women	Hypocaloric diet, education, cognitive–behavioral, physical activity	1	Placebo	188/138	−5.9 ± 7.6 kg	12
					2	Orlistat, 90 mg for 52 wk	187/140	Excluded because of low dosage	
					3	Orlistat, 180 mg for 52 wk	173/133	Excluded because of low dosage	
					4	Orlistat, 360 mg for 52 wk	181/126	−7.2 ± 5.5 kg	
Hollander et al., 1998 (47)	Orlistat	3	Adults	Hypocaloric diet	1	Placebo	159/115	−4.3 ± 7.2 kg	12
					2	Orlistat, 360 mg for 52 wk	163/139	−6.2 ± 6.5 kg	
Karhunen et al., 2000 (57)	Orlistat	2	Adult women	Hypocaloric diet	1	Placebo	36/19	−8.7 ± 6.3 kg	6
								−8.6 ± 6.3	12
					2	Orlistat, 360 mg for 104 wk	36/19	−11.2 ± 6.3 kg	6
								−13.1 ± 6.3 kg	12
Kelley et al., 2002 (56)	Orlistat	3	Adults	Hypocaloric diet, education, cognitive–behavioral	1	Placebo	276/128	−1.3 ± 3.2 kg	12
					2	Orlistat, 360 mg for 1 y	274/137	−3.9 ± 3.2 kg	
Krempf et al., 2003 (58)	Orlistat	2	Adult women	Hypocaloric diet	1	Placebo	350/350	−4.4 ± 10.4 kg	12
					2	Orlistat, 360 mg for 18 mo	346/346	−7.3 ± 9.6 kg	
Lindgarde et al., 2000 (71)	Orlistat	3	Adults	Hypocaloric diet, education, physical activity	1	Placebo	186/164	−4.3 ± 5.9 kg	12
					2	Orlistat, 360 mg for 1 y	190/159	−5.6 ± 5.2 kg	
Lucas et al., 2003 (60)	Orlistat	2	Adult women	Hypocaloric diet	1	Placebo	188/ND	−6.1 ± 6.9 kg	12
					2	Orlistat, 360 mg for 1 y	256/ND	−9.9 ± 6.4 kg	
Micic et al., 1999 (68)	Orlistat	3	Adult women	Hypocaloric diet	1	Placebo	59/49	−7.3 ± 6.3 kg	6
					2	Orlistat, 360 mg for 24 wk	60/50	−10.8 ± 6.3 kg	
Miles et al., 2002 (63)	Orlistat	2	Adults	Hypocaloric diet, education,	1	Placebo	261/254	−1.8 ± 3.6 kg	12
					2	Orlistat, 360 mg for 1 y	255/250	−4.7 ± 3.9 kg	
Muls et al., 2001 (53)	Orlistat	3	Adult women	Hypocaloric diet	1	Placebo	147/127	−1.9 ± 4.5 kg	6
					2	Orlistat, 360 mg for 24 wk	147/128	−4.7 ± 3.8 kg	
Naumov et al., 2002 (65)	Orlistat	1	Adults	Low-fat diet, no caloric restriction	1	Control, dosage and duration NR	15/15	−2.9 ± 3.0 kg	6
					2	Orlistat, 360 mg for 6 mo	15/15	−7.5 ± 2.5 kg	

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Appendix Table—**Continued**

Study, Year (Reference)	Medication	Quality Score†	Population	Co-Interventions	Arm	Intervention	Patients Who Entered Study/Patients Who Completed Study, *n/n*	Mean Weight Change ± SD	Follow-up, *mo*
Naumov et al., 2002 (65)	Orlistat	1	Adults	Low-fat diet, no caloric restriction	1	Control, dosage and duration NR	15/15	−2.9 ± 3.0 kg	6
					2	Orlistat, 360 mg for 6 mo	15/15	−7.5 ± 2.5 kg	
Reaven et al., 2001 (67)	Orlistat	2	Adults	None	1	Placebo	91/ND	−6.8 ± 6.4 kg	12
					2	Orlistat, 360 mg for 1 y	156/ND	−9.0 ± 7.9 kg	
Rissanen et al., 2001 (51)	Orlistat	2	Adult women	Hypocaloric diet	1	Placebo	ND/26	−7.5 ± 6.3 kg	6
								−7.2 ± 6.3 kg	12
					2	Orlistat, 360 mg for 12 mo	ND/25	−11.6 ± 6.3 kg	6
								−13.0 ± 6.3 kg	12
					2	Orlistat, 360 mg for 2 y	ND/3	–	–
Rosenfalck et al., 2002 (64)	Orlistat	3	Adult women	Hypocaloric diet	1	Placebo	ND/1	−3.8 ± 4 kg	12
					2	Orlistat, 360 mg for 2 y	ND/3	−8.6 ± 8.3 kg	
Rossner et al., 2000 (48)	Orlistat	3	Adult women	Hypocaloric diet, education	1	Placebo	243/136	−6.4 ± 6.7 kg	12
					2	Orlistat, 180 mg for 2 y	242/140	−8.5 ± 7.3 kg	
					3	Orlistat, 360 mg for 2 y	244/159	−9.4 ± 6.4 kg	
Shi Yi and Zhu Jun, 2001 (55)	Orlistat	2	Adults	Hypocaloric diet	1	Placebo	ND/142	−3.0 ± 6.3 kg	6
					2	Orlistat, 360 mg for 6 mo	986/286	−6.1 ± 6.3 kg	
Sjostrom et al., 1998 (49)	Orlistat	3	Adult women	Hypocaloric diet	1	Placebo	343/123	−6.1 ± 6.0 kg	12
					2	Orlistat, 360 mg for 2 y	345/133	−10.3 ± 6.3 kg	
Vidgren et al., 1999 (50)	Orlistat	3	Adult women	Hypocaloric diet	1	Placebo	38/ND	−7.8 ± 6.0 kg	12
					2	Orlistat, 360 mg for 12 mo	37/ND	−12 ± 8.2 kg	
Bray et al., 2003 (24)	Topiramate	4	Adult women	Cognitive–behavioral, antihypertensive medication, lipid-lowering medication	1	Placebo	75/48	−2.6% ± 4.8%	6
					2	Topiramate, variable dose for 24 wk	76/53	Excluded because it involved low/high dosage of the same medication	
					3	Topiramate, variable dose for 24 wk	75/48	−4.8% ± 4.8%	
					4	Topiramate, variable dose for 24 wk	76/49	−6.3% ± 4.8%	
					5	Topiramate, variable dose for 24 wk	78/44	Excluded because it involved low/high dosage of the same medication	
Caterson et al., 2003 (99)	Topiramate	2	Adult women	Hypocaloric diet, education, cognitive–behavioral, physical activity	1	Placebo	ND/97	1.8% ± 4.8%	11
					2	Topiramate, variable dose for 44 wk	ND/93	−5.2% ± 4.8%	

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Appendix Table—**Continued**

Study, Year (Reference)	Medication	Quality Score†	Population	Co-Interventions	Arm	Intervention	Patients Who Entered Study/Patients Who Completed Study, *n/n*	Mean Weight Change ± SD	Follow-up, *mo*
					3	Topiramate, variable dose for 44 wk	ND/98	−6.4% ± 4.8%	
Pud'homme et al., 2003 (97)	Topiramate	2	Adult men	None	1	Placebo	35/29	0.2% ± 3.2%	6
					2	Topiramate, variable dose for 24 wk	33/20	−5.8% ± 6.4%	
Rissanen et al., 2003 (96)	Topiramate	2	Adult women	Hypocaloric diet, education, cognitive–behavioral, physical activity	1	Placebo	ND/103	−2.9% ± 4.8%	15
					2	Topiramate, variable dose for 60 wk	ND/133	−9.1% ± 4.8%	
					3	Topiramate, variable dose for 60 wk	ND/123	−12% ± 4.8%	
					4	Topiramate, variable dose for 60 wk	ND/125	Excluded because it was a high-dosage study	
Stenlof et al., 2003 (95)	Topiramate	2	Adults	Hypocaloric diet, education, cognitive–behavioral, physical activity	1	Placebo	ND/137	−3.0% ± 4.8%	10
					2	Topiramate, variable dose for 40 wk	ND/127	−8.2% ± 4.8%	
					3	Topiramate, variable dose for 40 wk	ND/135	−10.0% ± 4.8%	
Tonstad et al., 2003 (98)	Topiramate	2	Adults	Hypocaloric diet, education, cognitive–behavioral, physical activity	1	Placebo	177/56	−1.9% ± 4.8%	7
					2	Topiramate, variable dose for 28 wk	176/49	−5.9% ± 4.8%	
					3	Topiramate, variable dose for 28 wk	178/53	−6.5% ± 4.8%	
					3	Topiramate, variable dose for 28 wk	178/53		

* ND = not designated; NR = not reported
† Jadad score ranging from 0 (lowest quality) to 5 (highest quality).
‡ For the 6.5-month analysis, arms 3 and 4 were combined and arm 2 was excluded because it had less than 6 months of follow-up. For the 11.5-month analysis, arms 2 and 3 were excluded because they had less than 11.5 months of follow-up.

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