Lifestyle Treatments in Randomized Clinical Trials of Pharmacotherapies for Obesity

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Abstract

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Objective: This meta-analysis evaluated the types of lifestyle treatments used in published obesity drug studies and assessed their contribution to weight losses associated with pharmacological interventions.

Research Methods and Procedures: Randomized, placebo-controlled, double-blind clinical trials of anti-obesity agents that are/were Food and Drug Administration-approved for the treatment of obesity (both prescription and over-the-counter), and drugs that are Food and Drug Administration-approved and are used off-label for obesity were included. Studies were located by computer searches of databases (e.g., Medline, PsychInfo) and reviewing tables of content/reference sections of journals, abstracts, previous reviews, past empirical studies, relevant book chapters, and recent issues of journals that regularly publish obesity research. In addition, a number of individuals who regularly publish in the obesity literature were asked to provide personal lists of obesity-drug studies. Based on the above criteria, a total of 108 randomized clinical trials were located.

Results: Balanced-deficit diets, low-calorie diets, and self-monitoring were the most used lifestyle treatments in published obesity studies. They were incorporated into 40.7%, 25%, and 23.1% of pharmacotherapy studies, respectively. Physical activity and other behavioral or psychotherapeutic interventions rarely were used. A substantial portion of weight loss experienced by patients was attributable to both "placebo effects" and to the lifestyle treatments.

Discussion: Obesity-pharmacotherapy trials do not use lifestyle treatments with the frequency expected based on the official positions of most professional organizations concerned with the comprehensive management of obesity.

Key words: anti-obesity agents, pharmacotherapy, lifestyle interventions

Introduction

Obesity and its associated healthcare costs have been rapidly increasing over the last 2 decades as nearly one-quarter of the U.S. population currently meets the definition of obese, i.e., body mass index (BMI) $\geq$ 30 kg/m^2 (1–3). There is growing recognition that obesity is a chronic disorder that is unlikely to be "cured," rather it requires long-term management not unlike type 2 diabetes or hypertension (4). In addition, the proliferation of research focused on biological (e.g., genetic and metabolic) obesity determinants has resulted in recognizing pharmacotherapy as a long-term management tool, which increasingly is being integrated into comprehensive obesity interventions (5).

Despite the growing interest in pharmacotherapy, lifestyle modification (i.e., psychosocial therapies, dietary interventions, and physical activity programs), has long played a central role in the management of obesity. In addition, lifestyle treatments often are considered to be the cornerstone of intervention (6–10). For example, the North American Association for the Study of Obesity (NAASO) (11), the National Task Force on the Prevention and Treatment of Obesity (12), and the National Heart, Lung, and Blood Institute Obesity Education Initiative (13) all state that pharmacotherapy is an adjunct to lifestyle modification approaches, not used in the absence of these modalities.

Several investigators have meta-analyzed the effectiveness of lifestyle interventions for the treatment of obesity. Haddock et al. (14) examined the effectiveness of obesity intervention targeted at children and adolescents by meta-analyzing 41 controlled outcome studies. Overall, they found that lifestyle interventions effectively produced weight loss at post-test and follow-up. In addition, they

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found that comprehensive treatment packages, i.e., those that contained behavior modification, dietary intervention, and physical activity, were the most effective and that the addition of behavior modification strategies (e.g., self-monitoring or stimulus control) to either diet or physical activity was better than those interventions without behavior modification techniques.

Garrow and Summerbell (15) and Miller et al. (16), examining 28 and >700 studies, respectively, meta-analyzed the effectiveness of diet, exercise, and diet + exercise on changes in body composition and weight loss among overweight and moderately obese subjects. Both reviews found that exercise alone produced the smallest weight losses, exercise helped preserve fat free mass when combined with diet, and that diet + exercise produced the best outcomes over the long-term. Unfortunately, the investigators also noted that the meta-analyzed studies tended to focus on a small subset of overweight to moderately obese individuals (e.g., BMI ranging from 25 to 37 kg/m^2). In addition, both reviews found that exercise-only studies tended to be conducted with even less generalized samples, i.e., most used populations with mean BMI < 30 kg/m^2. Both groups of investigators also noted the lack of evidence for long-term weight-loss maintenance, because most studies did not systematically report long-term follow-up data.

These meta-analyses have contributed to our knowledge about the effectiveness of lifestyle interventions and their limitations, e.g., they would require recurrent contact and would be costly and impractical to provide as part of a long-term obesity management program. No reviews have examined the quality and contributions of lifestyle interventions within the context of obesity pharmacotherapy. This is a notable gap in the scientific literature because of the increasing emphasis on combining pharmacotherapy with lifestyle interventions and the greater probability that drug interventions are likely to be provided to more seriously obese patients (8,11,17). Thus, the purpose of this meta-analysis was to evaluate the types of lifestyle interventions provided in obesity drug studies and to assess their contribution to weight loss.

Research Methods and Procedures

Literature Search

This report is part of a larger meta-analysis of the outcomes of randomized trials of obesity medications by Haddock et al. (18). For this report, we examined randomized clinical trials of anti-obesity medications that are/were Food and Drug Administration (FDA)-approved for the treatment of obesity (both prescription and over-the-counter) and drugs that are FDA-approved and are used off-label for obesity (12). The drugs selected were amphetamine, benzocaine, benzphetamine, dexfenfluramine, diethylpropion, fenfluramine, fluoxetine, mazindol, methamphetamine, orlistat, phendimetrazine, phentermine, phenylpropanolamine, sertraline, and sibutramine. We included fenfluramine and dexfenfluramine in the review because they were widely studied and used in clinical settings even though they were removed from the market in 1997. Not included were experimental obesity agents such as acarbose, beta-adrenoreceptor agonist (BRL 26830A), bromocriptine, buspar, cimetidine, fluvoxamine, human chorionic gonadotropin, human growth hormone, leptin, naloxone/naltrexone, or synthyroid. We also did not include nutritional supplements, which are defined by the Dietary Supplement Health and Education Act of 1994 (19) as products intended to supplement the diet and contain one or more of the following ingredients: 1) a vitamin; 2) a mineral; 3) an herb or other botanical; 4) an amino acid; 5) a dietary substance for use to supplement the diet by increasing the total dietary intake; or 6) a concentrate, metabolite, constituent, extract, or combination of any of the previously described ingredients. Examples of substances in this category include 5-hydroxytryptophan (HTP), ephedrine (ma huang), caffeine (guarana), chitosan, chromium (picolinate and nicotinate), dehydroepiandrosterone, garcinia cambogia/hydroxycitric acid, pyruvate, and St. John's Wort (hypericin).

Studies that met the following inclusionary criteria were included in the database: 1) the data were contained in published reports in peer-reviewed journals; 2) the data were for only human studies; 3) an English version of the study was available; 4) a direct comparison between an obesity-drug therapy designed to produce weight loss and another treatment modality or a control group of obese individuals was provided; 5) the participants were assigned randomly to treatment groups and the randomization scheme was not broken during assignment (i.e., some participants assigned randomly, some haphazardly); 6) groups were distinguishable on relevant parameters (e.g., drug type, use of lifestyle intervention); 7) the study provided sufficient outcome data to compute an effect size based on weight loss; and 8) the study was published on or before December 1999 (to provide a point to begin coding and data analysis).

Unfortunately, there were not enough studies providing long-term follow-up of intact treatments to be able to examine the long-term benefits of lifestyle treatments in obesity-medication trials. Therefore, analyses of study outcomes focus on post-test outcomes only. Finally, some studies used medications for weight maintenance after another obesity treatment, e.g., very low-calorie diet (VLCD), but were not used as the primary treatment for initial weight loss (20–22). We located a small number of maintenance articles and, although codeable, they were not included in the analyses.

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reference sections of journals, abstracts, previous reviews, past empirical studies, relevant book chapters, and recent issues of journals that regularly publish obesity research (e.g., *American Journal of Clinical Nutrition, International Journal of Obesity, Journal of the American Medical Association, Journal of Consulting and Clinical Psychology, Obesity Research*). In addition, a number of individuals who regularly publish in the obesity literature were asked to provide personal lists of obesity studies that address pharmacotherapy. Based on inclusionary criteria and the search procedures, a total of 108 independent, randomized clinical trials (published in 103 articles) were located.

Coding of Studies

Pharmacotherapy for Obesity: A Meta-Analysis of Control Trials Coding Manual containing the operational definitions of the variables used in this review was developed (available in Microsoft Word for Windows formatting by e-mail; please request from the first author). Reliability of coding was maintained by providing intensive training for the project assistants, including ~20 hours of didactic and coding practice. Each coder was required to reach perfect agreement with sample studies coded by the principal investigator (C.K.H.) before coding other studies. Finally, another project research assistant independently verified all coding. Because the majority of codes used in this review required little judgment (e.g., use of a diet or not, average weight of subjects, drug name), obtaining consistent coding was easily obtained. When parameters varied during the course of a study, an average of that parameter was coded.

We were unable to code a large number of studies that addressed obesity pharmacotherapy. Uncodable studies typically did not present data in a manner where group outcomes could be precisely distinguished (e.g., cross-over studies where data were only presented at the conclusion of the study) or did not present sufficient data to compute an effect size (typically these studies presented no data on outcome variability or information where outcome variance could be estimated) (18).

Lifestyle Treatment Components. Both broad (e.g., use of exercise) and specific (e.g., use of aerobic exercise) lifestyle treatment components were coded. These components were identified from articles in the behavioral weight-loss literature (6,8,9,14,23,24) and from consultation with scientists who study lifestyle approaches to weight loss. The broad treatment components included behavioral change strategies (behavior modification, psychotherapy, and cognitive behavior therapy), dietary intervention, and exercise programs. For the purpose of data analyses, we categorized lifestyle-treatment packages into those that used all three components (one or more of the three behavioral change strategies, diet, and exercise), two of the three components, one of the three components, or no lifestyle intervention. Lifestyle treatment components included specific behavioral modification strategies (i.e., self-monitoring, stimulus control, eating management, and contingency management), diets (i.e., VLCD, low-calorie diets, balanced-deficit diets, prepackaged food), and exercise programs (i.e., aerobics, weight-lifting, walking, calisthenics, and lifestyle exercise). In addition, we coded two measures of lifestyle treatment fidelity, the use of a lifestyle treatment manual, and the provision of formal training for the lifestyle interventionists. Definitions of each lifestyle treatment component are listed in Table 1.

Percentage of Weight Loss Due to Lifestyle Treatment. Given the small number of trials of any single drug and the insufficient variation in the lifestyle treatment offered across the trials, we were not able to examine the effect of various lifestyle treatments on the outcomes within medications. Therefore, to examine the effect of lifestyle treatments on outcome in drug trials, we estimated the percentage of the outcome that was due to the lifestyle components of the treatment in all drug vs. placebo comparisons. In the larger database, 95 studies provided drug vs. placebo comparisons with sufficient data to estimate the proportion of outcome due to the lifestyle components. These studies compared a drug + lifestyle treatment (or no lifestyle treatment in some studies) with a group of participants who were given a placebo + lifestyle intervention. Therefore, our estimates of the percentage of weight loss due to lifestyle treatments include the effect of placebo. We defined the percentage of the outcome due to lifestyle treatment as follows:

$$\text{Percentage of Outcome Due to Lifestyle Components} = 1 - \left[\frac{\text{Outcome in Drug Group} - \text{Outcome in Placebo Group}}{\text{Outcome in Drug Group}}\right]$$

When a single study provided more than one relevant outcome for an analysis, all within-study outcomes were aggregated to avoid statistical dependency.

Results

Characteristics of Selected Studies and Study Participants

Appendix 1 contains a complete list of studies included in the meta-analysis. Of the 108 clinical trials included, 102 were primarily concerned with pharmacologically induced weight loss. In the remaining six studies, weight loss was a secondary outcome, with factors such as macronutrient intake serving as the primary endpoint of concern. However, these six studies reported sufficient weight-loss data to be included in the study and used medications designed to induce weight loss. Publication dates of the studies ranged from 1960 to 1999, with 36.1% published in the 1990s, 12.0% in the 1980s, 42.6% in the 1970s, and 9.3% in the 1960s. Average age of the subjects included in the clinical trials was 40.7 years, although actual ages ranged from 5 to

Table 1. Definitions of lifestyle treatment components

Component	Definition
Behavioral modification	Behavioral techniques such as self-monitoring, stimulus control, eating management, or contingency management used.
Psychotherapy	Traditional psychotherapy (e.g., humanistic therapy, psychodynamic therapy) used. Excludes behavioral modification or cognitive behavioral therapy.
Cognitive behavioral therapy	Psychological treatments such as rational emotive behavior therapy or cognitive therapy. Therapy is a collaborative process of empirical investigation, reality testing, and problem solving.
Exercise	Any alteration in natural physical activity, even a suggestion to increase activity.
Diet	Any alteration in natural energy intake, even a suggestion to decrease consumption.
Self-monitoring	The participant formally monitors own behavior or activities.
Stimulus control	Strategies designed to alter cues leading to inappropriate eating, such as eating while watching television.
Eating management	Techniques specifically aimed at modifying the act of eating, such as eating slowly.
Contingency management	Rewards given for adhering to components of treatment or for weight loss.
Aerobics	Participants involved in vigorous, sustained activities such as running, jogging, swimming, dancing, etc.
Walking	Participants involved in a walking program.
Calisthenics	Exercises designed to develop muscular tone and promote physical well-being, such as sit-ups, toe-touches, leg raises, jumping jacks, and push-ups.
Weight-lifting	Exercises designed to increase muscle tone and mass such as lifting free weights and Nautilus.
Lifestyle exercise	Increased daily lifestyle activity such as taking stairs instead of elevators, walking to the store instead of driving, etc.
Low-calorie diet	Low-calorie diet defined as greater than 800 and less than 1200 kcal each day.
VLCD	Very low-calorie diet defined as 800 kcal each day or less.
Balanced-deficit diet	Energy-deficient diet of about 500 kcal from energy balance or described as between 1200 and 1500 kcal per day.
Prepackaged food	Participants were supplied food.
Treatment manual	A detailed, written description of the treatment procedures was provided to the lifestyle interventionists.
Formal training of lifestyle interventionists	Formal training of the lifestyle interventionists occurred or project principal investigator conducted lifestyle intervention.

77 years of age (see refs. 91 and 94 of Appendix 1). On average, 79.9% of participants in the clinical trials were female. Most studies (particularly earlier studies) did not report participant weight status in terms of BMI and did not report height. A majority of studies ($n = 75$) provided data on initial patient weight, which averaged 89.5 kg.

Use of Broad Lifestyle Components in Drug Studies

As can be seen in Table 2, the inclusion of lifestyle interventions in obesity-pharmacotherapy studies varied greatly over the last 40 years with one exception; most studies (i.e., >70%) included some form of dietary intervention.

Table 2. Percentage of studies including broad lifestyle components in clinical trial treatment packages

	Date of publication (number of studies)				
Component	**All (108)**	**1960s (10)**	**1970s (46)**	**1980s (13)**	**1990s (39)**
Behavioral modification	27.8	0	26.1	7.7	43.6
Psychotherapy	0.9	0	0	0	2.6
Cognitive behavioral therapy	0.9	0	2.2	0	0
Exercise	17.6	0	15.2	15.4	25.6
Diet	82.4	70.0	80.4	69.2	92.3
Treatment manual for lifestyle intervention	3.7	0	2.2	0	7.7
Formal training by lifestyle interventionists	49.1	60.0	47.8	23.1	56.4

The use of exercise interventions was infrequent (i.e., <20%) in the 1960s, 1970s, and 1980s but increased to be included in over one-quarter of all drug studies in the 1990s. Whereas the use of behavior modification strategies has varied by decade, with over one-quarter and nearly one-half of studies including these techniques in the 1970s and 1990s, respectively, the use of other psychosocial interventions (e.g., psychotherapy or cognitive behavioral therapies) is almost nonexistent. In addition, few studies used standardized treatment manuals for delivering the lifestyle interventions, although many studies provided formal training for the lifestyle interventionists.

Use of Specific Lifestyle Components in Drug Studies

Within the category of dietary component of lifestyle interventions, balanced-deficits were the most used interventions, and their use steadily increased over the 40 years of reviewed studies, from 10.0% of drug studies using them in the 1960s to 64.1% of drug studies incorporating them by the 1990s. During the same time-period, low-calorie diets declined in use, from a high of 50.0% in the 1960s to a 7.7% in the 1990s. The use of VLCDs and prepackaged foods was sparse and never exceeded 10% of drug studies.

None of the various forms of exercise were widely used in obesity-pharmacotherapy studies. For example, weight-lifting was not included in any of the selected studies. Aerobics, walking, and lifestyle exercise all were recent additions to obesity-pharmacotherapy studies, i.e., no studies reported including these components until the 1990s. Self-monitoring was the most used behavioral technique (8,25–27), with 0.0%, 23.9%, 15.4%, and 30.8% of studies using this procedure between the 1960s and the 1990s, respectively. None of the other behavior modification approaches were used with substantial frequency in obesity-drug studies, with a range of 3.7% and 4.6% of studies using stimulus control, eating management, and contingency management. Table 3 summarizes the use of specific lifestyle components.

Provider of the Lifestyle Treatment

The lifestyle treatment portion of the obesity treatment most often was delivered by the physician who also delivered the medication therapy in the clinical trial (33% of studies). Another 31.1% of the studies did not report who delivered the lifestyle intervention. The next two most-reported professions were nurses (10.4% of studies) and nutritionists (9.4% of studies). Interestingly, only one study used an individual specially trained in behavioral change (e.g., psychologist, psychiatrist, counselor) to deliver the lifestyle intervention.

Implementation of Lifestyle Treatment

Each study was coded as to the degree to which the implementation of the lifestyle treatment was assessed. That is, we coded whether the authors of the study documented that their participants actually received the lifestyle portion of the treatment package. Implementation was rated using the following three-point scale.

1. Documented appropriate implementation through quantitative data and these data were cogent (i.e., complete assessment of treatment as happened was what was planned to happen).
2. Partial implementation documentation. No formal assessment was made, but sufficient information was reported to conclude that the treatment was implemented as intended (e.g., an extended description of what occurred in treatment, experimenter supervised lifestyle interventionists, etc.).
3. Little or no effort was made to assess implementation. The author(s) merely name the techniques used and provided a short description.

Only 7.4% ($n = 8$) of the studies documented implementation through quantitative data. Another 24.1% ($n = 26$) provided partial implementation documentation, whereas 68.5% ($n = 74$) provided little or no documentation that the lifestyle treatment was delivered as intended.

Table 3. Specific dietary, physical activity, and behavioral-modification components included in clinical trial treatment package

	Date of publication (number of studies)				
Component	**All (108)**	**1960s (10)**	**1970s (46)**	**1980s (13)**	**1990s (39)**
VLCD	4.6	0	6.5	7.7	2.6
Low-calorie diet	25.0	50.0	39.1	7.7	7.7
Balanced-deficit diet	40.7	10.0	23.9	46.2	64.1
Prepackaged food	4.6	0	4.3	7.7	5.1
Aerobics	0.9	0	0	0	2.6
Weight-lifting	0	0	0	0	0
Walking	2.8	0	0	0	7.7
Calisthenics	0.9	0	0	7.7	0
Lifestyle exercise	0.9	0	0	0	2.6
Self-monitoring	23.1	0	23.9	15.4	30.8
Stimulus control	3.7	0	6.5	7.7	0
Eating management	4.6	0	4.3	7.7	5.1
Contingency management	3.7	0	8.7	0	0

Percentage of Outcome Due to Lifestyle Components

We also evaluated what proportion of the weight loss produced in obesity-drug studies was attributable to the inclusion of lifestyle modification interventions, i.e., the percentage of the outcome that was due to the lifestyle components of the treatment in all drug vs. placebo comparisons. As can be seen in Figure 1, in drug trials without any lifestyle component, 28.3% of the weight loss was attributed to the effect of the placebo, suggesting a modest "placebo effect" in obesity-pharmacotherapy trials.

Figure 1 also illustrates the proportion of weight loss in the drug groups attributable to one, two, or three lifestyle intervention components including the effects of placebos. It is notable that there was not a consistent dose-response effect, i.e., any two components that were included with drug treatments contributed the most to the overall weight loss (53.7%), whereas one or three lifestyle components only contributed to 45.8% and 46.5% of the weight losses among patients receiving obesity pharmacotherapy, respectively.

Finally, we matched each of the principal lifestyle components against each other to evaluate which components' inclusion (in addition to embedded placebo effects) was most important for inducing weight loss beyond the effects of pharmacotherapy. For example, Figure 1, column 1, illustrates the proportion of weight loss attributable to the inclusion of behavioral change strategies (45.3%) vs. those that did not (i.e., studies that may have included any or none of the other lifestyle components; 45.3%) among patients receiving obesity pharmacotherapy. Thus, diet interventions were the single strongest lifestyle component because they were responsible for 49.5% of weight loss among patients receiving drug treatments vs. 26.5% for those studies that did not have that component. The percentage of outcome due to lifestyle components and placebo in those studies that did not include a dietary component (i.e., second set of bars in Figure 1) was similar to that for studies including no lifestyle components (i.e., placebo only, last bar in Figure 1). This is likely because of significant overlap in these two sets of studies.

Discussion

We found that lifestyle treatments, with the exception of dietary components, have not been widely used in randomized, placebo-controlled obesity-drug trials. For example, with the exception of studies in the 1990s, behavioral modification techniques were used in $<30\%$ of trials, whereas other psychotherapeutic and cognitive behavioral interventions were used in $<1\%$ of reviewed trials. Even in the 1990s, less than one-half of studies reported using behavioral strategies.

Even more interesting was the lack of use of exercise interventions (17.0% overall) or lifestyle modification treatment manuals (3.8%) that might ensure some treatment standardization. When we examined specific lifestyle treatments, a balanced-deficit diet (41.4%) was the most used dietary component and overall lifestyle intervention. Low-calorie diets were second (24.5%). Self-monitoring was third overall (i.e., it was used in 23.5% of reviewed trials)

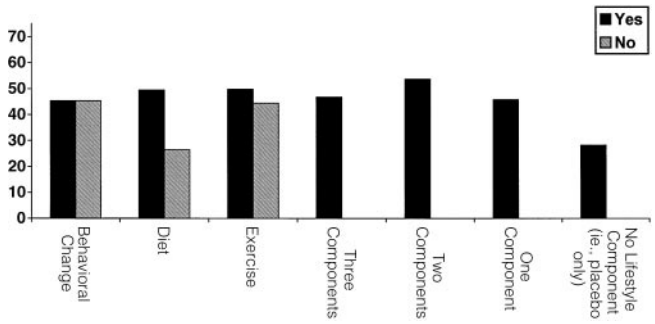

Figure 1: Percentage of outcome due to inclusion of broad lifestyle components and placebo. Only studies reporting weight-loss data separately for each group in the trial were included in the analyses. Behavior Change included studies that offered behavior modification, psychotherapy, and cognitive behavioral therapy.

and it was the most used behavioral modification component. None of the other specific lifestyle treatments were implemented in more than 5% of obesity drug trials. It was particularly interesting how infrequently lifestyle exercise and walking were incorporated into drug studies, even in the 1990s. These data suggest that the design of obesity drug trials are deficient and do not provide comprehensive treatments. This is despite organizational calls to approach obesity from a multidisciplinary perspective and provide multicomponent treatments (8,11,13,28).

Previous reports on lifestyle interventions found that most lifestyle obesity intervention trials had been conducted with middle-aged, overweight to moderately obese women (15,16). Our meta-analysis also found that many randomized obesity drug trials were conducted with patients who were moderately obese, women, and in their 40s. This trend of obesity trials using similar populations suggests that their outcomes may not be generalized to the larger population of obesity patients who seek treatment, particularly those with more severe obesity (i.e., BMI $>$ 35 kg/m^2).

One-third of the reviewed obesity-drug studies did not identify who provided the lifestyle treatment. Among those that did, the physician who also provided the drug delivered the lifestyle treatment(s). Whereas this model is probably a more efficient and pragmatic way to provide treatment in primary care settings (28), physicians often are not trained in nutrition, exercise, or behavior modification (29–33). In addition, this practice is contrary to the positions espoused by most obesity organizations calling for multidisciplinary treatment teams (13). Thus, it is unclear how well the lifestyle interventions were implemented and whether or not outcomes would be improved if individuals with specific training and expertise in these areas provided the treatments.

A substantial portion of weight loss experienced by patients in obesity drug trials was attributable to both "placebo effects" and to the lifestyle treatments, with dietary interventions (plus, to some degree, placebo effects) accounting for the most weight loss when compared with other lifestyle treatments. In addition, we found that including more lifestyle components did not necessarily account for more weight loss. These data suggest that lifestyle interventions, particularly behavior modification interventions, were not particularly effective in producing weight loss. However, these findings should be viewed within the context that most studies did not use any lifestyle intervention other than providing patients with a balanced-deficit or low-calorie diet. In addition, in those studies using behavior modification techniques, less than one-quarter used self-monitoring, which was the most frequently used technique. Also, $<$10% of studies quantitatively documented the implementation of lifestyle interventions while 68.5% provided little or no documentation of any kind. This suggests that lifestyle interventions, and behavior modification techniques in particular, were not implemented in a way that would maximize their impact on weight loss. In contrast, the lack of attention to implementation might imply to patients that they were not important or necessary for weight loss success.

There are several limitations to this report. We were only able to code lifestyle interventions if they were discussed somewhere in the drug trial. If investigators included a lifestyle intervention but did not name or describe it in the article, we could not code it. However, we believe that we captured all lifestyle interventions that were described. Investigators of future drug trials should fully describe their interventions so that studies can be better evaluated. In addition, investigators often provided very limited and sparse descriptions of their lifestyle interventions; thus, we were unable to estimate the "dose" of lifestyle treatment that patients received in drug trials, i.e., most studies did not include information about the amount of time in counseling, number of sessions, amounts or types of dietary or exercise intervention, etc.

At a minimum, it is recommended that future obesity pharmacotherapy studies consistently provide details about the nature and types of lifestyle treatments used, who provided them and how they were trained, the amount of time that patients received the intervention (e.g., per week, per month, etc.), and document implementation and adherence. Investigators also are encouraged to use standardized lifestyle packages like "The Lifestyle, Exercise, Attitudes, Relationships, Nutrition (LEARN) Program for Weight Management" (34), "The LEARN Program for Weight Management: Special Medication Edition" (35), or "Living with Exercise" (36). In addition, future studies also might use designs that more directly assess the contribution of lifestyle modification components. For example, such a study might include randomization to placebo or wait-list control, drug-only, lifestyle-only, and lifestyle + drug groups. Stunkard et al. (37) approximated this type of design, although they did not specify how patients were allotted to the following groups: 1) structured group behavior

therapy alone; 2) pharmacotherapy (fenfluramine) + nonspecific supportive group counseling; 3) behavior therapy plus medication; 4) doctor's office pharmacotherapy (i.e., pharmacotherapy and advice by a physician that included diet and exercise instructions); and 5) a wait-list control group. At the end of the 6-month treatment period, patients in the combined behavior + medication group lost the most weight (15.3 ± 1.2 kg), followed by patients in the medication + nonspecific group counseling (14.5 ± 1.1 kg), behavior therapy alone (10.9 ± 1.0 kg), and doctor's office with medication (6.0 ± 1.7 kg). The wait-list group gained weight (1.3 ± 1.3 kg). At 18-months follow-up, patients in the behavior therapy alone arm regained less weight than those in the combined behavior + medication or medication + nonspecific group counseling arms.

More recently (and beyond the time frame of our meta-analysis), Wadden et al. (38) compared the following treatments in a randomized 1-year trial: 1) drug treatment (sibutramine) + instructions to increase physical activity and consume a 1200 to 1500 kcal diet; 2) drug treatment + instructions to increase physical activity and consume a 1200 to 1500 kcal diet + behavioral strategies to achieve activity and dietary change; and 3) drug treatment + instructions to increase physical activity and consume a 1000 kcal portion-controlled diet for the first 4 months + instructions to increase physical activity and consume a 1200 to 1500 kcal diet + behavioral strategies to achieve activity and dietary change. Patients in the drug-only arm (group 1) experienced significantly greater attrition and the lowest weight loss at the end of treatment (3.8 ± 6.1 kg), when compared with patients in the combined treatments (11.1 ± 10.5 and 16.6 ± 7.5 kg for groups 2 and 3, respectively). Thus, these designs suggest that lifestyle interventions, including the use of behavioral strategies, are important contributors to weight loss and should be included and documented in pharmacotherapy drug trials. The above measures will greatly improve the ability of researchers to evaluate the usefulness of various lifestyle treatment components within the context of obesity pharmacotherapy.

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Appendix 1—Studies Included in the Meta-Analysis

Lettered references represent data from a single study published in multiple articles.

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