Published in final edited form as:

Obes Rev. 2009 May ; 10(3): 333–341. doi:10.1111/j.1467-789X.2009.00567.x.

Attrition from Randomized Controlled Trials of Pharmacological Weight Loss Agents: A Systematic Review and Analysis

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Summary

Clinical trials of obesity treatments have been limited by substantial dropout. Participant-level variables do not reliably predict attrition, and study-level variables have not yet been examined. We searched MEDLINE and identified 24 large randomized controlled trials of weight loss medications. These trials were comprised of 23 placebo and 32 drug groups. Two authors independently extracted the following for each treatment group: treatment received; design characteristics (inclusion of a lead-in period, selection of participants with weight-related comorbidities, study location, and number of study visits); sample characteristics (sample size, % female, and mean baseline age and BMI); and attrition (total, adverse event [AE] related, and non-AE-related) at 1 year. The primary outcome was total attrition, which was significantly related to treatment (i.e., 34.9%, 28.6%, 28.3%, and 35.1% in placebo, orlistat, sibutramine, and rimonabant groups, respectively, $p < .0001$). In adjusted multivariable models, total attrition was significantly lower in groups that completed a pre-randomization lead-in period than in those that did not (29.1% vs. 39.9%, $p < .01$). Gender also was significantly related to total attrition; groups with more women had higher dropout ($p < .01$). The pattern was similar for predicting non-AE-related attrition. Findings suggest ways to design studies that maximize retention.

Keywords

Pharmacotherapy; obesity; attrition; retention; study design

Introduction

Attrition is the bane of clinical trials. Nowhere is this problem more apparent than in trials of weight loss medications, as underscored by two recent commentaries.¹⁻² Although there are

multiple analytic methods for addressing the problem of missing data, none is a replacement for measuring the weight of all randomized participants, and each has significant shortcomings.

Completers-only analyses, for instance, can result in an inflated estimate of efficacy because lack of weight loss may be a reason for attrition. Thus, most large trials report results from intent-to-treat (ITT) analyses, with the last observation carried forward (LOCF) in the case of missing data. LOCF imputation, however, does not account for the likelihood of regaining lost weight after discontinuing treatment and can overestimate weight loss efficacy.²⁻³ A more conservative imputation method – a modification of LOCF – assumes a constant rate of weight regain (e.g., 0.3 kg/month) and figures it into the imputed value.⁴⁻⁵ This procedure can lead to an over- or underestimation of efficacy, depending on the timing of, and reason for, dropout. Perhaps the most stringent imputation procedure is known as baseline observation carried forward (BOCF), which assumes no change from randomization for participants who drop out of the study.¹ However, given the high rate of attrition from many trials of pharmacological weight loss agents, this imputation method may underestimate a drug's effect. Model-based imputation methods assume that missing data are due to random factors and, thus, are also significantly flawed.¹

Limiting attrition is, therefore, an important consideration in obtaining reliable and valid study results. If persons at greatest risk of dropping out can be identified, they may be targeted for proactive retention efforts. Although individual studies have identified some demographic and behavioral characteristics that predict attrition, results have been equivocal.⁶⁻⁹ An alternative approach would be to design studies in ways to maximize retention. It is unknown, however, whether study design characteristics – for example, including a pre-randomization lead-in period or targeting a certain patient population – can limit attrition. A systematic review and synthesis of the research is needed.

The present investigation summarized rates of attrition from large randomized controlled trials of weight loss drugs with adult participants and at least 1 year's duration. The primary objective was to identify treatment, design, and sample characteristics that were associated with attrition from all causes. In secondary analyses, the same variables were examined as predictors of attrition that was either related or unrelated to adverse events. Adherence to treatment is a separate (but related) issue that is infrequently reported in clinical trials and, thus, is not addressed in the present study.

Method

Search Strategy

Published studies were identified using the MEDLINE electronic database. Trade and generic names of frequently studied weight loss medications (including agents used off-label for weight loss) were entered as search terms. These terms were intersected with terms related to obesity and weight loss. Only human studies, published in English, before September 2007 were returned. (The detailed search strategy is available from the first author upon request.) This search yielded 1,777 published papers, including original research articles, reviews, case studies, and editorials.

Inclusion Criteria

Only randomized controlled trials were considered for inclusion in the present study. Additional inclusion criteria were: 1) participants were overweight or obese adults (age ≥ 18 years); 2) the intervention included administration of orlistat, sibutramine, rimonabant, phentermine, fenfluramine, the phentermine-fenfluramine combination, dex-fenfluramine, topiramate, or bupropion; 3) at least 100 participants were randomized into each study

condition; 4) change in weight (expressed in kg or % of initial weight) was reported; 5) attrition was reported; and 6) study duration was at least 1 year post-randomization. One author (EAG) examined study abstracts and/or texts to determine whether studies met inclusion criteria, and another author (ANF) reviewed the first's determinations to verify eligibility.

Twenty-nine studies, published from 1989 to 2006, met all inclusion criteria. The study drugs included orlistat, sibutramine, rimonabant, topiramate, and dex-fenfluramine. We decided to exclude the dex-fenfluramine and topiramate trials, because there was only one study of each.¹⁰⁻¹¹ Additionally, we excluded two orlistat studies and one sibutramine trial because they tested the drugs' efficacy for weight loss maintenance, not weight loss.¹²⁻¹⁴ Thus, 24 randomized controlled trials of orlistat, sibutramine, or rimonabant were included in the analyses described below.¹⁵⁻³⁹ (Although rimonabant has been withdrawn from the market, we retained the rimonabant studies because they were well designed and they met all inclusion criteria for our investigation.) All but one study was placebo-controlled; the excepted study varied the calorie target of the accompanying diet plan.³⁶ For another investigation, data were extracted from two separate papers.³⁰⁻³¹

Data Extraction

Two authors (ANF and MLB) independently reviewed each paper in detail to extract data for each treatment condition across the 24 included studies. The independent variables of interest were treatment (i.e., placebo, orlistat, sibutramine, or rimonabant) and various study design and sample characteristics. Study design characteristics included: 1) location (North America, Europe, or multiple/other continents); 2) whether participants were selected based on the presence of a weight-related comorbidity (e.g., type 2 diabetes); 3) presence or absence of a pre-randomization lead-in (i.e. "run-in") period; 4) number of post-randomization study visits; and 5) number of post-randomization visits in which lifestyle counseling was provided (i.e., "lifestyle visits"). Sample characteristics included mean age and body mass index (BMI) at baseline, as well as sample size and the percentage of female participants in each study group. Sample characteristics were based on the ITT population of each study group, for whom those characteristics were reported. (Most included studies defined the ITT population as those participants who took at least one dose of study medication and returned for at least one visit after randomization. Although this definition of ITT is clearly not ideal, we have elected to use it to remain consistent with the language of the included trials.)

The dependent variables extracted pertained to study attrition at 1 year after randomization. The primary outcome variable was total attrition from all causes, which was calculated as number of dropouts at 1 year divided by number of randomized participants. Attrition related to adverse events (i.e., AE-related attrition), when reported, was extracted separately. From total and AE-related attrition, we calculated attrition *not* related to adverse events (i.e., non-AE-related attrition). AE-related and non-AE-related attrition were secondary outcomes.

Data Analysis

A summary of each included study is provided in tabular form. Means and standard errors of all continuous variables and frequencies of categorical variables are provided in the results section. In all inferential analyses, the unit of analysis was the treatment group.

To model the fact that each study contributed two or three groups to these analyses, mixed models were fit to: 1) compare baseline sample characteristics (i.e., % female, age, and BMI) between treatments (i.e., placebo, orlistat, sibutramine, and rimonabant); and 2) determine relationships of treatment, design, and sample characteristics to total, AE-related, and non-AE-related attrition. All mixed models included one level of random effect to adjust for study variability and at least one fixed effect to adjust for sample size. Where treatment was not the

independent variable of interest, analyses included a second fixed effect to adjust for treatment. Least square means $\pm$ standard errors were derived from the mixed models and are presented for all analyses.

Continuous characteristics (% female, age, weight, BMI, and number of postrandomization study and lifestyle visits) were first included in the mixed models in continuous form to assess significant relationships with attrition. To characterize important relationships, $\beta \pm$ standard errors are presented for continuous variables that were significantly associated with attrition ($p < .05$) or those that showed a trend ($p < .10$). Additionally, those variables were dichotomized using median split, and the least square means $\pm$ standard errors of attrition for the lower and upper 50th percentile of these continuous variables are presented.

The final multivariable mixed models presented are a result of two modeling steps. The first step consisted of a mixed model that simultaneously included, in addition to adjustment for sample size and treatment group, all variables that were found to be significantly ($p < .05$) or marginally ($p < .10$) associated with the attrition outcome in univariable analyses. The final multivariable model included only those variables that were significantly associated ($p < .05$) with the outcome in the initial multivariable model. All analyses were conducted using the statistical software package, SAS 9.1 (SAS Institute, Cary, NC, USA).

Results

Included Studies

Of the 24 studies included, 16, 4, and 4 were trials of orlistat, sibutramine, and rimonabant, respectively. Seven were conducted in North America, 12 in Europe, and 5 in multiple or other continents. In 11 studies, all participants were selected for the presence of a weight-related comorbidity. Eighteen studies included a lead-in period, which, in every instance, included single-blind administration of a placebo (i.e., the participant was blinded) for 2 to 5 weeks prior to randomization. The mean $\pm$ standard error length of the lead-in period of 2.5 ± 0.4 weeks, including six studies with no lead-in period. The mean number of post-randomization study visits during year 1 was 13.5 ± 0.9 . The number of post-randomization lifestyle visits (i.e., visits in which diet/exercise counseling was provided) could be extracted from 12 studies. These trials included a mean of 11.8 ± 1.9 such visits in year 1. A summary of study characteristics is shown in Table 1.

In total, 18,918 participants were included in 23 placebo groups and 32 active drug groups. Across treatment groups, the mean age of participants was 47.9 ± 0.8 years, and BMI was 35.5 ± 0.2 kg/m². On average, $69.4 \pm 1.9\%$ of participants were women. Table 2 displays sample characteristics for groups that received placebo, orlistat, sibutramine, and rimonabant, regardless of dose.

The mean total attrition rate across the 55 treatment groups was $32.8 \pm 1.6\%$. In the 48 groups from which AE-related attrition and non-AE-related attrition could be extracted, means were $7.8 \pm 0.6\%$ and $26.7 \pm 1.5\%$, respectively.

Univariable Predictors of Attrition

Results from univariable analyses are summarized in Table 3. All models were adjusted as described above.

Treatment—The treatment participants received was significantly related to all attrition outcomes. Total attrition was significantly higher in groups that received placebo than in those that received orlistat and sibutramine. Rimonabant groups differed only from orlistat groups; rimonabant groups had significantly greater total attrition.

Placebo, orlistat, and sibutramine groups all had similar rates of AE-related attrition. AE-related attrition was significantly higher in rimonabant groups than placebo and orlistat groups.

Non-AE-related attrition was significantly higher in placebo groups, compared with orlistat and sibutramine groups, which did not differ from each other. Rimonabant groups did not differ from any other groups with respect to non-AE-related attrition.

Lead-in period—There was significantly lower total and non-AE-related attrition in study groups that included a lead-in period than in those that did not. Presence or absence of a lead-in period was not associated with AE-related attrition.

Comorbidity as an inclusion criterion—Selection of participants based on the presence of a weight-related comorbidity was related to marginally lower total attrition and significantly lower non-AE-related attrition. AE-related attrition did not differ by whether or not a weight-related comorbidity was an inclusion criterion.

Location—The location in which the study was conducted was marginally associated with total attrition. Location, however, was unrelated to both AE-related and non-AE-related attrition.

Number of study visits and “lifestyle” visits—None of the 1-year attrition outcomes was related to the number of post-randomization visits included in the first year. Furthermore, no attrition variables were related to the number of visits in which lifestyle counseling was provided.

Percentage of women—The percentage of women in the study group (measured continuously) was significantly related to total attrition ($\beta = 0.33 \pm 0.13$) and non-AE-related attrition ($\beta = 0.37 \pm 0.13$). To further characterize these relationships, the percentage of women was dichotomized using the median split procedure (median = 77.8%) into low (mean = 57.3%) and high (mean = 82.0%) groups. Subsequent comparisons showed that low-percentage female groups had significantly less total attrition ($28.9 \pm 2.6\%$ vs. $34.3 \pm 2.5\%$) and non-AE attrition ($22.0 \pm 2.8\%$ vs. $28.2 \pm 2.6\%$) than high-percentage female groups ($p < .05$).

Age—Mean age of study groups, as a continuous variable, was unrelated to all attrition outcomes. Thus, we did not perform median splits to test low vs. high groups.

BMI—Although mean BMI at baseline (measured continuously) was not significantly related to total attrition, it was associated with both AE-related ($\beta = -0.86 \pm 0.40$) and non-AE-related attrition ($\beta = 2.51 \pm 1.19$). However, after using the median split procedure (median = 35.7 kg/m²) to categorize BMI into low (mean = 34.3 kg/m²) and high (mean = 36.8 kg/m²), we found no significant differences between low- and high-BMI groups in AE-related attrition (9.1 ± 0.9 vs. 7.3 ± 1.0 , $p = .18$) or non-AE attrition (23.3 ± 2.9 vs. 28.0 ± 3.1 , $p = .23$).

Multivariable Predictors of Attrition

All predictors that were significantly or marginally related to total or non-AE-related attrition in the univariable analyses were entered simultaneously into an initial multivariable model for that type of attrition. Both models were adjusted for treatment and sample size (which also were the standard covariates included in the univariable models). Final multivariable models, adjusted for the same covariates, included predictors that significantly predicted attrition in the initial multivariable models. Results are summarized in Table 4. Multivariable models for AE-related attrition were unnecessary because mean BMI was the only significant univariate predictor, other than treatment.

The initial multivariable model for total attrition included presence/absence of a lead-in period, whether a comorbidity was an inclusion criterion, study location, and percentage of women in the sample. The final multivariable model suggests that, when adjusting for all measured factors related to total attrition, the presence of a lead-in period and having a smaller percentage of women in the sample were significantly related to lower total attrition.

The initial multivariable model for non-AE-related attrition included presence/absence of a lead-in period, whether a comorbidity was an inclusion criterion, percentage of women in the sample, and mean sample BMI. As was true of total attrition, the final multivariable model for non-AE-related attrition indicated that groups that had a lead-in period and those that had a lower percentage of women had significantly lower non-AE-related attrition after adjustment for all other relevant predictors.

Discussion

This research represents the first attempt to characterize factors related to attrition across a variety of randomized controlled trials of weight loss drugs. Previous studies have focused exclusively on participants' psychosocial or demographic characteristics within individual trials and have yielded largely mixed results.

In our analysis of group-level and study-level variables, we found that treatment was strongly related to total attrition. Dropout rates were highest among groups treated with placebo or rimonabant, and lowest among those treated with orlistat or sibutramine. Adverse events appear to have contributed to the equivalence between placebo and rimonabant groups with respect to total attrition. Rimonabant groups had 5% greater AE-related attrition and 5% lower non-AE-related attrition than placebo groups. We suspect that the relationship between treatment and total attrition was, in part, a function of weight loss; participants who lost less weight may have been more likely to drop out. Unfortunately, however, we could not control for weight loss in our analyses for two reasons: 1) LOCF weight loss data are confounded by attrition; and 2) multicollinearity between weight loss and treatment was too high to include both predictors in the same analyses.

Inclusion of a lead-in period was a study design feature that was significantly related to lower total attrition in both univariable and fully-adjusted multivariable analyses. These lead-in periods consisted of single-blind administration of a placebo for 2 to 5 weeks. The majority of lead-ins also included a low-calorie diet prescription. In many studies, however, the only stated criterion to continue on to randomization was participants' achieving ~70% medication (i.e., placebo) adherence, as determined by unused doses returned to the clinic. Regardless of its length, nature, or requirements, the inclusion of a lead-in period allows for more rigorous evaluation of potential participants than is possible with a telephone screening or a single on-site visit. Candidates with suboptimal motivation, commitment, or availability can be excluded prior to randomization. The disadvantage of this approach is that it limits researchers' ability to generalize findings to less adherent individuals.

A lead-in period also presents candidates a truer picture of study participation (i.e., requirements) than the informed consent document can provide. For example, the Look AHEAD study – a large randomized trial of lifestyle modification in adults with type 2 diabetes – included an intensive screening process that required candidates to keep detailed records of food intake and physical activity for 2 weeks.⁴⁰ This lead-in period simulated an important aspect of study participation (i.e., self-monitoring of energy intake and expenditure). Approximately 5% of Look AHEAD candidates failed this behavioral criterion,⁴¹ which may well have reduced attrition by a similar amount.

The selection of participants with a weight-related comorbidity was marginally related to lower attrition in univariable analyses but was not related in more fully adjusted models. Attrition may have been somewhat lower in participants with weight-related comorbidities because of their greater perceived urgency for weight loss and lifestyle change, or because of stronger support from family members and health care providers. Concern about the health consequences of obesity may have increased their threshold for side-effects and other potential hassles related to study participation, such as attending clinic visits. However, the effect of this study design feature was not strong enough to predict attrition when adjusting for lead-in and gender composition of the sample.

Of the sample characteristics we examined, the percentage of females treated was the only significant predictor of total attrition in fully adjusted models. This relationship appeared primarily attributable to non-AE-related attrition because gender composition of the sample was not associated with AE-related attrition. Although gender was often a constant or was not examined in previous studies that sought to identify predictors of attrition,⁸⁻⁹ at least one investigation found that women were more likely than men to drop out of a weight loss trial.⁷ The present findings suggest that targeting males for recruitment in weight loss studies may not only enhance generalizability of findings, but also improve retention.

We were surprised that neither the number of study visits, nor the number of visits in which lifestyle modification counseling was provided, was related to attrition. We expected that more frequent contact with the clinic and more intensive lifestyle counseling would facilitate retention, as these factors were associated with greater weight loss in some pharmacotherapy trials.^{4,42} Perhaps the costs of visiting the clinic (e.g., time, effort, money) balanced whatever benefits the increased contact may have afforded. Additionally, the lack of association between study visits and attrition may be attributed to limited variability in the former. Nineteen of the 24 included studies had at least monthly visits and only one averaged more than two visits per month. We also note that most reports provided a limited description of the adjunctive lifestyle modification offered, which precluded our considering the quality of the intervention in our analyses. Simple prescriptive advice was coded as equivalent to protocol-driven behavioral or dietary counseling. We suspect that the use of empathic staff (e.g., dietitians) who are trained and supervised in the delivery of a sound, structured intervention, may reduce attrition from weight loss trials. Several large studies that included a lifestyle modification component and followed this approach (e.g., Look AHEAD, the Diabetes Prevention Program, PREMIER) retained well over 90% of participants at 1 year and beyond.^{41,43-47}

The chief liability of our report is that several factors that may have accounted for significant variance in attrition (e.g., socioeconomic status, psychosocial stress, interactions with study staff, compensation for participation, efforts to increase retention) were not measured or reported in most of the studies we examined. Thus, we could not include all potentially relevant predictors in our analyses. Additionally, our investigation did not address the issue of adherence, which, like participant retention, is critical to evaluating the efficacy of an intervention. Unfortunately, clinical trials rarely report adherence variables, such as percentage of medication doses taken or visits attended.

Although our use of group-level data reduced power and may have masked significant findings, this approach can be considered a strength of our investigation. By examining group-level data, we were able to look beyond individual demographic or psychosocial predictors of attrition to examine the roles of study design features and treatment. We also examined AE-related and non-AE-related attrition separately, under the assumption that the latter is more modifiable than the former. This separation not only emphasized that non-AE-related attrition (e.g., lost to follow-up, withdrawn consent) is the greater contributor to total attrition but also that non-AE-related attrition is more responsive to study design features than is AE-related attrition.

Future studies may seek to replicate the present findings in randomized controlled trials of medications used to treat other medical conditions. Given the resources and effort that sponsors, clinicians, and patients all invest in clinical research, reducing attrition is in the interest of all parties. Moreover, the analytic and interpretive problems posed by attrition underscore that maximizing retention of participants is in the best interest of clinical science.

Acknowledgements

This work was supported in part by a Merck grant to Fabricatore and by National Institutes of Health (NIH) grants K23 DK070777 and K24 DK065018 to Fabricatore and Wadden, respectively. Fabricatore has served as a consultant to Pfizer and has received research support (for this study) from Merck. Wadden serves on the Advisory Boards of Merck, Novo Nordisk, and Orexigen and has received research support from Merck, Orexigen, Pfizer, and Vivus. Erondy, Heymsfield, and Nguyen are employed by Merck. The other authors have no potential conflicts to declare.

References

1. Ware JH. Interpreting incomplete data in studies of diet and weight loss. *New Engl J Med* 2003;348:2136–2137. [PubMed: 12761370]
2. Simons-Morton DG, Obarzanek E, Cutler JA. Obesity research – limitations of methods, measurements, and medications. *JAMA* 2006;295:826–828. [PubMed: 16478906]
3. Svetkey LP, Stevens VJ, Brantley PJ, Appel LJ, Hollis JF, Loria CM, Vollmer WM, Gullion CM, Funk K, Smith P, Samuel-Hodge C, Myers V, Lien LF, Laferriere D, Kennedy B, Jerome GJ, Heinith F, Harsha DW, Evans P, Erlinger TP, Dalcin AT, Coughlin J, Charleston J, Champagne CM, Bauck A, Ard JD, Aicher K. Weight Loss Maintenance Collaborative Research Group. Comparison of strategies for sustaining weight loss: the Weight Loss Maintenance randomized controlled trial. *JAMA* 2008;299:1139–1148. [PubMed: 18334689]
4. Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Phelan S, Cato RK, Hesson LA, Osei SY, Kaplan R, Stunkard AJ. Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med* 2005;353:2111–2120. [PubMed: 16291981]
5. Marinilli Pinto A, Gorin AA, Raynor HA, Tate DF, Fava JL, Wing RR. Successful weight-loss maintenance in relation to method of weight loss. *Obesity* 2008;16:2456–2461. [PubMed: 18719680]
6. Wadden, TA.; Letizia, KA. Predictors of attrition and weight loss in patients treated by moderate and severe caloric restriction. In: Wadden, TA.; VanItallie, TB., editors. *Treatment of the Seriously Obese Patient*. Guilford; New York: 1992. p. 383-410.
7. Honas JJ, Early JL, Frederickson DD, O'Brien MS. Predictors of attrition in a large clinic-based weight-loss program. *Obes Res* 2003;11:888–894. [PubMed: 12855759]
8. Teixeira PJ, Going SB, Houtkooper LB, Cussler EC, Metcalfe LL, Blew RM, Sardinha LB, Lohman TG. Pretreatment predictors of attrition and successful weight management in women. *Int J Obes* 2004;28:1124–1133.
9. Dalle Grave R, Calugi S, Molinari E, Petroni ML, Bondi M, Compare A, Marchesini G. QUOVADIS Study Group. Weight loss expectations in obese patients and treatment attrition: an observational multicenter study. *Obes Res* 2005;13:1961–1969. [PubMed: 16339128]
10. Guy-Grand B, Apfelbaum M, Crepaldi G, Gries A, Lefebvre P, Turner P. International trial of long-term dexfenfluramine in obesity. *Lancet* 1989;2:1142–1145. [PubMed: 2572857]
11. Wilding J, Van Gaal L, Rissanen A, Vercruysse F, Fitchet M. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects. *Int J Obes* 2004;28:1399–1410.
12. Hill JO, Hauptman J, Anderson JW, Fujioka K, O'Neil PM, Smith DK, Zavoral JH, Aronne LJ. Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: a 1-year study. *Am J Clin Nutr* 1999;69:1108–1016. [PubMed: 10357727]
13. Richelsen B, Tonstad S, Rössner S, Toubro S, Niskanen L, Madsbad S, Mustajoki P, Rissanen A. Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients: a 3-year randomized, placebo-controlled study. *Diabetes Care* 2007;30(1):27–32. [PubMed: 17192328]

14. James WP, Astrup A, Finer N, Hilsted J, Kopelman P, Rössner S, Saris WH, Van Gaal LF. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. *Lancet* 2000;356:2119–2125. [PubMed: 11191537]
15. Hollander PA, Elbein SC, Hirsch IB, Kelley D, McGill J, Taylor T, Weiss SR, Crockett SE, Kaplan RA, Comstock J, Lucas CP, Lodewick PA, Canovatchel W, Chung J, Hauptman J. Role of orlistat in the treatment of obese patients with type 2 diabetes: a 1-year randomized double blind study. *Diabetes Care* 1998;21:1288–1294. [PubMed: 9702435]
16. Sjöström L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, Krempf M. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients: European Multicentre Orlistat Study Group. *Lancet* 1998;352:167–172. [PubMed: 9683204]
17. Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, Heimburger DC, Lucas CP, Robbins DC, Chung J, Heymsfield SB. Weight control and risk factor reduction in obese subjects treated for two years with orlistat: a randomized controlled trial. *JAMA* 1999;281:235–242. [PubMed: 9918478]
18. Finer N, James WP, Kopelman PG, Lean ME, Williams G. One-year treatment of obesity: a randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor. *Int J Obes* 2000;24:306–314.
19. Hauptman J, Lucas C, Boldrin MN, Collins H, Segal KR. Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med* 2000;9:160–167. [PubMed: 10693734]
20. Lindgärde F. The effect of orlistat on body weight and coronary heart disease risk profile in obese patients: The Swedish Multimorbidity Study. *J Intern Med* 2000;248:245–254. [PubMed: 10971792]
21. Rössner S, Sjöström L, Noack R, Meinders AE, Nosedá G. Weight loss, weight maintenance, and improved cardiovascular risk factors after two years treatment with orlistat for obesity: European Orlistat Obesity Study Group. *Obes Res* 2000;8(1):49–61. [PubMed: 10678259]
22. Smith IG, Goulder MA. The Sibutramine Clinical Study 1047 Team. Randomized placebo-controlled trial of long-term treatment with sibutramine in mild to moderate obesity. *J Fam Pract* 2001;50:505–512. [PubMed: 11407998]
23. Broom I, Wilding J, Stott P, Myers N. The UK Multimorbidity Study Group. Randomised trial of the effect of orlistat on body weight and cardiovascular disease risk profile in obese patients: UK Multimorbidity Study. *Int J Clin Pract* 2002;56:494–499. [PubMed: 12296610]
24. Hanefeld M, Sachse G. The effects of orlistat on body weight and glycaemic control in overweight patients with type 2 diabetes: a randomized, placebo-controlled trial. *Diabetes Obes Metab* 2002;4:415–423. [PubMed: 12406041]
25. Kelley DE, Bray GA, Pi-Sunyer FX, Klein S, Hill J, Miles J, Hollander P. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: a one-year randomized controlled trial. *Diabetes Care* 2002;25:1033–1041. [PubMed: 12032111]
26. Miles JM, Leiter L, Hollander P, Wadden T, Anderson JW, Doyle M, Foreyt J, Aronne L, Klein S. Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. *Diabetes Care* 2002;25:1123–1128. [PubMed: 12087008]
27. Krempf M, Louvet JP, Allanic H, Miloradovich T, Joubert JM, Attali JR. Weight reduction and long-term maintenance after 18 months treatment with orlistat for obesity. *Int J Obes* 2003;27:591–597.
28. Hauner H, Meier M, Wendland G, Kurscheid T, Lauterbach K. Weight reduction by sibutramine in obese subjects in primary care medicine: the SAT study. *Exp Clin Endocrinol Diabetes* 2004;112:201–207. [PubMed: 15127325]
29. Kaukua JK, Pekkarinen TA, Rissanen AM. Health-related quality of life in a randomised placebo-controlled trial of sibutramine in obese patients with type II diabetes. *Int J Obes* 2004;28:600–605.
30. Porter JA, Raebel MA, Conner DA, Lanty FA, Vogel EA, Gay EC, Merenich JA. The long-term outcomes of sibutramine effectiveness on weight (LOSE Weight) study: evaluating the role of drug therapy within a weight management program in a group-model health maintenance organization. *Am J Manag Care* 2004;10:369–376. [PubMed: 15209480]
31. Malone DC, Raebel MA, Porter JA, Lanty FA, Conner DA, Gay EC, Merenich JA, Vogel EA. Cost-effectiveness of sibutramine in the LOSE Weight Study: evaluating the role of pharmacologic weight-loss therapy within a weight management program. *J Manag Care Pharm* 2005;11:458–468. [PubMed: 15998163]

32. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004;27(1):155–161. [PubMed: 14693982]
33. Berne C. The Orlistat Swedish Type 2 diabetes Study Group. A randomized study of orlistat in combination with a weight management programme in obese patients with Type 2 diabetes treated with metformin. *Diabet Med* 2005;22:612–618. [PubMed: 15842517]
34. Després JP, Golay A, Sjöström L. Rimonabant in Obesity-Lipids Study Group. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* 2005;353:2121–2134. [PubMed: 16291982]
35. Swinburn BA, Carey D, Hills AP, Hooper M, Marks S, Proietto J, Strauss BJ, Sullivan D, Welborn TA, Caterson ID. Effect of orlistat on cardiovascular disease risk in obese adults. *Diabetes Obes Metab* 2005;7:254–262. [PubMed: 15811142]
36. Toplak H, Ziegler O, Keller U, Hamann A, Godin C, Wittert G, Zanella MT, Zúñiga-Guajardo S, Van Gaal L. X-PERT: weight reduction with orlistat in obese subjects receiving a mildly or moderately reduced-energy diet: early response to treatment predicts weight maintenance. *Diabetes Obes Metab* 2005;7:699–708. [PubMed: 16219013]
37. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rössner S. RIO-Europe Study Group. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: one-year experience from the RIO-Europe study. *Lancet* 2005;365:1389–1397. [PubMed: 15836887]
38. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. The RIO-North America Study Group. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 2006;295:761–775. [PubMed: 16478899]
39. Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF. RIO-Diabetes Study Group. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. *Lancet* 2006;368:1660–1672. [PubMed: 17098084]
40. The Look AHEAD Research Group. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Cont Clin Trials* 2003;24:610–628.
41. The Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. *Diabetes Care* 2007;30:1374–1383. [PubMed: 17363746]
42. Digenio A, Mancuso J, Dimitratos C, Dvorack R. Comparison of five different methods of delivering a comprehensive non-pharmacological weight loss program in patients on sibutramine. *Obesity* 2005;13:A4.
43. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New Engl J Med* 2002;346:393–403. [PubMed: 11832527]
44. Diabetes Prevention Program Research Group. The Diabetes Prevention Program (DPP): description of the lifestyle intervention. *Diabetes Care* 2002;25:2165–2171. [PubMed: 12453955]
45. Look AHEAD Research Group. The Look AHEAD Study: a description of the lifestyle intervention and the evidence supporting it. *Obesity* 2006;14:737–752. [PubMed: 16855180]
46. Svetkey LP, Harsha DW, Vollmer WM, Stevens VJ, Obarzanek E, Elmer PJ, Lin PH, Champagne C, Simons-Morton DG, Aickin M, Proschan MA, Appel LJ. Premier: a clinical trial of comprehensive lifestyle modification for blood pressure control: rationale, design, and baseline characteristics. *Ann Epidemiol* 2003;13:462–471. [PubMed: 12875806]
47. Elmer PJ, Obarzanek E, Vollmer WM, Simons-Morton D, Stevens VJ, Young DR, Lin PH, Champagne C, Harsha DW, Svetkey LP, Ard J, Brantley PJ, Proschan MA, Erlinger TP, Appel LJ. PREMIER Collaborative Research Group. Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. *Ann Intern Med* 2006;144:485–495. [PubMed: 16585662]

Table 1

Summary of studies of weight loss medications included in the analysis.

Study	Drug	Active:Placebo Groups*	Sample**	Comorbidity Selected	Location	Lead-In Weeks	Study Visits†	Lifestyle Visits‡	Total Attrition
Hollander 1998	Orlistat	1:1	321††	T2DM	N Amer	5	20	—	21.8%
Sjöström 1998	Orlistat	1:1	688	None	Europe	4	12	—	20.4%
Davidson 1999	Orlistat	1:1	892	None	N Amer	4	17	4	33.7%
Finer 2000	Orlistat	1:1	218	None	Europe	4	15	15	39.0%
Hauptman 2000	Orlistat	2:1	635	None	N Amer	4	15	4	32.8%
Lindgärde 2000	Orlistat	1:1	376	CHD risk	Europe	2	10	10	14.1%
Rössner 2000	Orlistat	2:1	718	None	Europe	4	11	11	28.1%
Smith 2001	Sibutramine	2:1	485	None	Europe	2	12	—	47.2%
Broom 2002	Orlistat	1:1	522	CV Risk	Europe	2	12	—	34.7%
Hanefeld 2002	Orlistat	1:1	369	T2DM	Europe	4	12	—	31.1%
Kelley 2002	Orlistat	1:1	535	T2DM	N Amer	0	18	—	51.8%
Miles 2002	Orlistat	1:1	504	T2DM	N Amer	0	12	—	39.7%
Krempf 2003	Orlistat	1:1	696	None	Europe	2	12	—	31.3%
Hauner 2004	Sibutramine	1:1	348	None	Europe	0	10	7‡	40.1%
Kaukua 2004	Sibutramine	1:1	236††	T2DM	Europe	2	12	12	11.0%
Porter 2004/Malone 2005	Sibutramine	1:1	501	None‡‡	N Amer	0	27	27	42.3%
Torgerson 2004	Orlistat	1:1	3277	None	Europe	0	19	19	15.8%
Berne 2005	Orlistat	1:1	220	T2DM	Europe	2	4	—	13.6%
Deprés 2005	Rimonabant	2:1	1033††	Dyslipidemia	Other	4	13	13	37.9%
Swinburn 2005	Orlistat	1:1	339††	Hypercholes./HTN/T2DM	Other	4	13	—	20.6%
Toplak 2005	Orlistat	2:0	430	None	Other	0	7	7	38.6%
Van Gaal 2005	Rimonabant	2:1	1507	None‡‡	Other	2	13	13	39.0%
Pi-Sunyer 2006	Rimonabant	2:1	3040	None‡‡	N Amer	4	14	—	47.4%
Scheen 2006	Rimonabant	2:1	1045	T2DM	Other	4	13	—	33.7%

* Studies with two active groups tested different doses of the same medication.
** Number of participants in ITT population, unless otherwise specified.

[†] Post-randomization, in year 1. Within each study, all treatment groups received the same number of study visits and lifestyle visits.

^{††} Number of participants randomized.

[‡] Participants were offered 16 additional lifestyle visits, but acceptance was not reported.

^{‡‡} Participants with a BMI < 30 kg/m² were required to have a weight-related comorbidity, but because the full sample was not selected for the presence of a comorbid condition, these studies were coded as not selecting for comorbidities.

// The “Other” category included studies conducted in Australia and New Zealand, or at clinical sites on multiple continents (i.e., some combination of North America, South America, Europe, and Australia).

— Data could not be extracted from paper.

Abbreviations: N Amer = North America; T2DM = Type 2 diabetes mellitus; CHD = coronary heart disease; CV = cardiovascular; Hypercholes = Hypercholesterolemia; HTN = Hypertension.

Table 2

Sample characteristics by treatment group.

	All Groups (n = 55)	Placebo (n = 23)	Orlistat (n = 19)	Sibutramine (n = 5)	Rimonabant (n = 8)
Women in Study Group (%)	69.4 ± 1.9	68.6 ± 3.1	69.1 ± 3.1	68.7 ± 3.5	69.0 ± 3.5
Age (years)	47.9 ± 0.8	48.0 ± 1.2	48.1 ± 1.2	47.4 ± 1.3	49.2 ± 1.7
Baseline BMI (kg/m ²)	35.5 ± 0.2	35.5 ± 0.3	35.6 ± 0.3	36.0 ± 0.4	35.5 ± 0.4

Note: N refers to the number of study groups that received a given treatment. Values in cells are adjusted means ± standard errors. There were no significant differences among groups.

Table 3

Results from univariable models to predict attrition at 1 year.

Independent Variable	Attrition		
	Total	AE-Related	Non-AE-Related
Treatment	$p < .0001$	$p = .05$	$p < .001$
Placebo	$34.9 \pm 2.4_a$	$6.2 \pm 0.8_a$	$30.5 \pm 2.5_a$
Orlistat	$28.6 \pm 2.5_b$	$7.8 \pm 1.0_a$	$22.9 \pm 2.6_b$
Sibutramine	$28.3 \pm 3.3_{bc}$	$8.1 \pm 1.8_{ac}$	$22.9 \pm 3.9_b$
Rimonabant	$35.1 \pm 3.2_{ac}$	$11.0 \pm 1.6_{bc}$	$25.3 \pm 3.6_{ab}$
Lead-In Period	$p = .05$	$p = .69$	$p = .002$
Yes	$29.1 \pm 2.6_a$	8.4 ± 0.9	$22.0 \pm 2.1_a$
No	$39.9 \pm 4.5_b$	7.8 ± 1.4	$36.2 \pm 3.6_b$
Comorbidity as Inclusion Criterion	$p = .06$	$p = .61$	$p = .05$
Yes	26.9 ± 3.3	8.7 ± 1.1	$20.7 \pm 3.1_a$
No	35.9 ± 3.1	7.9 ± 1.0	$29.9 \pm 3.0_b$
Study Location	$p = .10$	$p = .93$	$p = .27$
North America	38.8 ± 4.1	8.6 ± 1.4	31.1 ± 4.3
Europe	27.3 ± 3.2	7.9 ± 1.1	22.0 ± 3.5
Other	32.6 ± 4.8	8.3 ± 1.5	24.7 ± 4.6
Number of Study Visits	$p = .19$	$p = .97$	$p = .11$
Number of Lifestyle Visits	$p = .80$	$p = .17$	$p = .26$
Women in Study Group (%)	$p = .02$	$p = .32$	$p = .01$
Mean Age of Study Group	$p = .14$	$p = .92$	$p = .13$
Mean Body Mass Index of Study Group	$p = .40$	$p = .04$	$p = .05$

Note. The p values reported refer to the significance of each independent variable. For categorical variables, mean attrition rates ($\pm$ standard errors) also are reported for each subgroup. Within each type of attrition, subgroup means marked with different subscripts were significantly different from each other at $p < .05$.

Table 4

Results from initial and final multivariable models to predict total and non-AE-related attrition.

Variable	Total Attrition		Non-AE Attrition	
	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Initial Multivariable Model				
Sample Size	.82	.37	.26	.62
Treatment	11.62	< .0001	10.28	< .001
Lead-In Period	5.49	.03	15.15	< .001
Comorbidity as Inclusion Criterion	.20	.67	.91	.35
Study Location	2.74	.08		
Women in Study Group (%)	6.09	.02	6.56	.02
Mean BMI of Study Group			.06	.81
Final Multivariable Model				
Sample Size	1.56	.22	.11	.74
Treatment	12.02	< .0001	10.14	< .001
Lead-In	7.76	< .01	14.48	.001
Women in Study Group (%)	9.92	< .01	9.49	< .01