Cost-Effectiveness of Sibutramine in the LOSE Weight Study: Evaluating the Role of Pharmacologic Weight-Loss Therapy Within a Weight Management Program

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ABSTRACT

OBJECTIVE: No previous studies conducted in the United States have evaluated the cost-effectiveness of drug therapy when used in conjunction with a weight management program (WMP) for treatment of obesity. The objective was to compare the cost-effectiveness of sibutramine plus a structured WMP versus only a structured WMP in both overweight and obese individuals. The core WMP was a physician-supervised, multidisciplinary program for which each enrollee paid $100 out of pocket.

METHODS: A cost-effectiveness analysis was performed based upon the results of a previously published randomized controlled trial conducted within a managed care organization. The target population for this study was obese or overweight persons. The perspective of the study was that of a managed care organization. The intervention consisted of subjects receiving a WMP with or without sibutramine. The primary outcomes of this study were (a) absolute change in body weight and percentage change in body weight over 12 months, (b) change in obesity-related and total medical costs from 12 months prior to enrollment through 12 months after enrollment, and (c) cost-effectiveness in terms of cost per pound of weight loss. All costs were adjusted to 2004 dollars using the respective components of the consumer price index for each medical service or medication.

RESULTS: A total of 501 evaluable subjects were enrolled in the study, with 281 receiving sibutramine plus a structured WMP and 220 receiving only the structured WMP. The mean ± SD weight loss was significantly greater in the sibutramine (13.7 ± 15.5 pounds, 4.8%) group than in the nondrug group (5 ± 13.2 pounds, 2.2%) (P < 0.001). The change in obesity-related total cost was a median increase of $408 for the sibutramine group compared with $31 for the nondrug group (P < 0.001). The change in total health care cost was a median $1,279 increase in the sibutramine group compared with $271 for the nondrug group (P < 0.001). Adding sibutramine to the WMP increased the total cost by $44 per additional pound of weight loss (95% confidence interval, 42-46). Sensitivity analyses found that the results were sensitive to the price of sibutramine, whereas varying the cost of clinic visits did not substantially change the results.

CONCLUSION: Patients enrolled in a WMP receiving sibutramine had greater weight loss and decrease in body mass index at greater cost than did patients enrolled in the same program who did not receive sibutramine. There were no observed savings in total health care resource utilization or cost in the sibutramine group compared with the nondrug group.

KEYWORDS: Obesity, Sibutramine, Cost-effectiveness, Cost analysis

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In 2000 almost 55% of adults in the United States aged 20 years or older were overweight (body mass index [BMI] of ≥ 25 kg/m²). More recent data suggest that, in 2003, all states in the United States had greater than 15% of their populations who were considered obese (BMI of > 30 kg/m²), with 4 states (Alabama, Indiana, Mississippi, and West Virginia) reporting that more than 25% of their residents were obese.

The incidence of chronic diseases, including hypertension, hyperlipidemia, type 2 diabetes, coronary artery disease, stroke, gallbladder disease, musculoskeletal disorders, and some cancers, increases with increasing weight. Direct health care costs for chronic diseases related to obesity were estimated at $47.5 billion in 2002 dollars. When indirect costs associated with obesity are considered, the estimated total cost of obesity in the United States was more than $99 billion in 1995 dollars.

Eighty-five percent of the costs of obesity are considered attributable to 5 diseases: hypertension, type 2 diabetes, coronary artery disease, hyperlipidemia, and stroke.

The relationship between obesity and other chronic conditions has been well studied. Persons with BMI values of 25 kg/m² or more at increased risk of hypertension, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, etc.
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Methods

Study Design, Setting, and Population

The LOSE Weight study was conducted at KPCO, a group-model health maintenance organization (HMO). In the year 2000, KPCO provided health care for a diverse population of more than 350,000 members in the Denver-Boulder-Longmont metropolitan area; about 50,000 of these individuals were Medicare beneficiaries. At the time of this study, more than 90% of members were enrolled in a prepaid, traditional HMO insurance plan; benefits did not differ between Medicare and non-Medicare enrollees. About 96% of health plan members had prescription drug benefits that did not include coverage of medications used to treat obesity.

The LOSE Weight study was a prospective, randomized trial involving overweight and obese patients enrolled in the WMP. The methods and clinical outcomes of the LOSE Weight study are described in detail elsewhere.22 Briefly, study enrollment occurred from January 1999 through June 2000. Eligible patients were aged 18 years or older and had either BMI ≥30 kg/m^2 or BMI of 27-29.9 kg/m^2 with one or more comorbidities, including diabetes, hypertension, and/or hyperlipidemia. Subjects were randomized to receive sibutramine or no drug therapy, but all patients participated in the WMP. Participating subjects were randomly assigned to either the drug or nondrug group using a computer-generated random numbers table. Study assignments were placed in envelopes that were opened upon completion of the baseline visit.

The core WMP was a physician-supervised, multidisciplinary program for which enrollees paid $100. It included 5 monitored care visits with a prevention specialist and attendance at 2 or more group-format weight management seminars. At WMP monitored-care visits, weight, height, body fat, vital signs, and waist and hip circumference values were obtained. Patient education and goal setting for diet, exercise, and other lifestyle modifications were provided by a prevention specialist. Monitoring for efficacy and safety of weight-loss medications occurred, if applicable. All study subjects also participated in 2 education programs offered by the American Heart Association: Slim for Life ($70) and Active for Life ($70). These programs each had 10 classes. Study subjects incurred a total of

respiratory problems, and various forms of cancer (endometrial, breast, prostate, and colon).2 There is also a variety of complications that arise from obesity, including pregnancy complications, stress incontinence, depression, and menstrual irregularities.2 Numerous studies have found that obese persons are more likely than nonobese persons to have hypertension.8-12 Data from the International Study of Sodium, Potassium, and Blood Pressure (INTERSALT) found that higher body weight was associated with a 3 mm Hg increase in systolic and 2.3 mm Hg increase in diastolic blood pressures.11 This increase is associated with an increased risk of coronary heart disease of 12% and a 24% increase in the risk of stroke. There is a clear relationship between obesity and coronary heart disease.13-15

Several studies have shown that increased BMI is associated with a higher prevalence of metabolic syndrome. Data from the Third National Health and Nutrition Examination Survey (NHANES III) show a marked increase in the prevalence of metabolic syndrome as a function of BMI.16 In persons with a BMI greater than 30, the prevalence of metabolic syndrome was almost 50% in white and Mexican American women. Among white and Mexican American men, the prevalence of metabolic syndrome was greater than 50% when BMI was 31 or greater. This same study also found that metabolic syndrome is more common in white and Mexican American persons as compared with black persons. The odds ratio of having metabolic syndrome was greater than 5 for overweight males and females as compared with normal-weight persons. These odds ratios sharply increased when BMI was greater than 30 (25.2 for men and 14 for women). There also is a strong association between obesity and diabetes.17-19 The risk of diabetes was found to increase by 25% for each additional BMI unit over 22 kg/m^2.20 A more recent study found that 56% of new type 2 diabetes in the Health Professionals Follow-up Study could be attributable to a weight gain of greater than 7 kg.21

The relationship between obesity and the myriad health consequences challenges managed care organizations. Most people believe that obesity is due more to caloric intake than genetic and disease-mediated factors, despite evidence to the contrary.22 With an increasing population of obese members, managed care organizations are encountering increased pressure to offer solutions to the problem, including the decision as to whether antiobesity drugs should be included in the prescription drug benefit.

Because strategies to effectively lower body weight are needed, we conducted a study at Kaiser Permanente of Colorado (KPCO) to evaluate the effectiveness of obesity drug therapy: the Long-term Outcomes of Sibutramine Effectiveness on Weight (LOSE Weight) study.23,24 This prospective, randomized 12-month study assessed the impact of sibutramine (Meridia) in combination with the Kaiser Permanente Weight Management Program (WMP) compared with the WMP alone. The results of the primary clinical end point of weight loss were the focus of a previous publication.24 A secondary end point of the LOSE Weight study was an evaluation of health care resource utilization and associated costs.

Results of health care resource utilization, costs, and the cost-effectiveness of sibutramine in the context of the LOSE Weight study are described here. In this current study, we evaluated the cost-effectiveness of sibutramine plus the structured WMP versus only the structured WMP. We hypothesized that there were no differences in resource use and costs between the group of patients who received sibutramine compared with the nonsibutramine group and that the incremental cost-effectiveness would be no different from zero.
$240 in financial commitments to be included in the WMP and American Heart Association programs, the same costs as patients enrolled in these programs who were not study participants. Study participants who completed 6 months of the study received a $50 gift check. Those patients who completed 12 months of the study received an additional $100 gift check.

Patients randomly assigned to sibutramine paid the usual pharmacy price for the drug at the time of dispensing and were later reimbursed 75% of this price upon presenting the prescription receipt. Enrollment in theLOSE Weight study did not influence the routine medical care these patients received. Study subjects continued to see primary care and specialty physicians at their discretion throughout the study. The Kaiser Foundation Research Institute Institutional Review Board approved this study.

The primary measure of effectiveness for the clinical analysis was the mean change in body weight from baseline to 6 months after enrollment; the secondary measure of clinical effectiveness was the mean change in body weight from baseline to 12 months. For the economic analysis, we examined change in body weight through 12 months. The last observation carried forward was used for missing data. Because change in body weight can be influenced by the initial starting weight, a secondary measure of effectiveness used in this analysis was the percentage change in body weight.

Economic End Points

The economic analysis in theLOSE Weight study measured resource utilization over a 24-month period, including the 12 months before and after study enrollment. Utilization data were derived from electronic medical records and administrative claim and clinical databases maintained and used by KPCO for providing patient care and tracking medical expenses. The analysis examined the use of medical resources from the perspective of a managed care organization. Evaluation of health care resource utilization included outpatient visits (including medical office and emergency department visits), hospitalizations, professional services claims (e.g., oxygen, ambulance, outside physician referrals), and prescription medications. We have included total costs in the analysis to capture adverse events that may arise due to treatment with sibutramine. In addition, we also analyzed obesity-related utilization and costs.

Obesity-related and nonobesity-related health care resource utilization was evaluated. Expert panels comprising 3 to 5 physicians, 2 clinical pharmacists, and a health promotion specialist determined whether outpatient visits and hospitalizations were related to obesity for the time periods of 12 months before and 12 months after study enrollment. Each evaluator conducted an independent review and was blinded to the identity of the treatment arm. All experts were asked to independently classify medication use as “1” (most likely related to obesity, points = 1), “2” (possibly related to obesity, points = 2), or “3” (not related to obesity, points = 3). For a resource to be considered obesity-related, a majority of the panel members must have assigned a value of 1, and no expert could assign a value of 3. Outpatient visits were considered related to obesity if the panel determined that the visit was related to either obesity or to adverse events associated with obesity therapy. Examples of conditions related to obesity included diabetes mellitus (type 2), pure hypercholesterolemia, hypertension, coronary arteriosclerosis, and gout. A hospitalization was considered related to obesity if one or more of the first 4 discharge diagnosis codes (International Classification of Diseases, Ninth Revision, Clinical Modification) on the hospital claim were determined by the panel to be obesity-related.

To establish if medications were obesity-related, an expert panel consisting of 3 physicians and clinical pharmacists was asked to determine if the medications were obesity-related. Similar to medical encounters, medications were rated by experts as “1” (most likely related to obesity, points = 1), “2” (possibly related to obesity, points = 2), or “3” (not related to obesity, points = 3). The same scoring rules applied to medications when determining if a drug was used to treat an obesity-related condition. Examples of medications classified as being obesity-related included antidiabetics, antihypertensives, dyslipidemic therapies, and nitroglycerin.

Resource Units and Costs
Cost estimates for outpatient visits and hospitalizations were estimated using Medicare’s resource-based relative value scale fee schedule and the reimbursement rates of diagnosis-related groups. The cost of each service was calculated by multiplying the number of units by a standard price per unit. Costs from Medicare fee schedules were based on 1998 reimbursement rates. Costs for professional claims were based on billed amounts. The cost for prescription medications, including the study drug sibutramine, was based on average wholesale price at the time of dispensing. All costs were adjusted to 2004 dollars using the respective components of the consumer price index for each medical service or medication.

Economic Analysis
Incremental cost-effectiveness ratios were constructed using mean change in total costs between the 2 groups divided by the mean change in body weight. Incremental cost-effectiveness was also calculated on percentage change in body weight. Sensitivity analyses were conducted using median measures of cost and effect because cost data were skewed. Comparisons also were made between groups with respect to obesity-related care. In addition, the cost of sibutramine was removed from the analysis to examine the impact of sibutramine costs. Sensitivity analyses also were conducted by increasing clinic costs upward by 50%.

Statistical Analysis
The analysis was conducted using an intention-to-treat population.
Evaluable subjects were defined as those subjects who retained membership in KPCO for at least 12 months, received at least one dose of sibutramine (for the drug group), and had at least one recorded weight 4 weeks after being randomly assigned to the treatment groups. For those persons with fewer than 12 months of clinical data, the last observation was carried forward in the analyses. The study was powered to detect a 10% difference in change in body weight between the groups using a 2-tailed alpha of 0.05 and power of 75%. The estimated sample size necessary was 285 subjects per group.

Univariate analyses were performed on clinical and economic variables, and nonparametric statistical procedures were used for variables that were not normally distributed. Therefore, instead of reporting mean and standard deviations for skewed data, we report median and 5th and 95th percentiles. For incremental cost-effectiveness ratios, a nonparametric bootstrap with 1,000 replications was performed using Stata Version 8 (College Station, TX). Determination of 95% confidence intervals were made using the bias-corrected approach.25

Regression analysis was used to isolate the effect of the medications and cost of therapy while controlling for other factors. Variables in the regression analysis included age, gender, chronic diseases, BMI, and study treatment arm. Chronic diseases were determined using the chronic disease score (CDS) method of Clark et al.26 The regression equation used was: COST = A + B1AGE + B2 CDS + B3 BMI + B4 ARM + B5 BMI*CDS + B6 AGE*CDS + B7 GENDER + ERROR where A represents the intercept, ARM represents study group assignment, COST was the dependent variable and represents the total medical care cost for the 12-month period after enrollment, and each \( B_n \) represents the coefficient for each specified variable. This analysis was conducted using SAS REG procedure (SAS Version 9.0, SAS Institute, Cary, NC).

**Results**

A total of 1,564 subjects were invited to participate in the study, with 976 (62%) not participating due to lack of interest. Figure 1 displays the enrollment and completion rates for the study. Of the 588 patients enrolled in the study, 501 (85%) were eligible for evaluation based on the intent-to-treat analysis. Of these, 220 subjects received the WMP-only and 281 received sibutramine plus WMP. Patient baseline demographic characteristics are in Table 1. Of the evaluable patients, those assigned to the sibutramine plus WMP were significantly older and had higher BMI values than did those receiving only the WMP. This difference was likely related to the fact that persons who were enrolled in the study and randomly assigned to the nondrug group prematurely discontinued the study because they were seeking the medication. The distribution of BMI is shown in Figure 2. There were 57 (26%) receiving only WMP and 94 (33%) receiving sibutramine plus WMP who had a baseline BMI greater than 40 (\( P=0.07 \)). Six percent of the sample was aged 65 years or older, evenly distributed between the 2 groups (\( P=0.47 \)).

<table>
<thead>
<tr>
<th>Evaluable Patients</th>
<th>Intention-to-Treat Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,564 Screened</td>
<td>296 Included in Intention-to-Treat Analyses</td>
</tr>
<tr>
<td>976 Did Not Meet Inclusion Criteria or Were Not Interested</td>
<td>292 Assigned to Weight Management Program Only</td>
</tr>
<tr>
<td>588 Randomized Into 2 Groups</td>
<td>281 Included in Intention-to-Treat Analyses</td>
</tr>
<tr>
<td>192 Completed Trial</td>
<td>220 Included in Intention-to-Treat Analyses</td>
</tr>
<tr>
<td>147 Completed Trial</td>
<td>5 Adverse Events</td>
</tr>
<tr>
<td>0 Lost to Follow-up</td>
<td>0 Lack of Efficacy</td>
</tr>
<tr>
<td>16 Protocol Violation</td>
<td>80 Lost to Follow-up</td>
</tr>
<tr>
<td>21 Withdrew Consent</td>
<td>21 Protocol Violation</td>
</tr>
<tr>
<td>44 Withdrew Consent</td>
<td>0 Adverse Events</td>
</tr>
</tbody>
</table>

*All evaluable patients were included in the intention-to-treat analyses. Evaluable subjects were defined as subjects who retained membership with Kaiser Permanente of Colorado for the 6- and 12-month follow-up periods, received at least one dose of study medication (if randomized to sibutramine), and had a body weight recorded at least 4 weeks after randomization.

Figure 3 displays the body weight of the subjects by gender over time for the 2 treatment groups. The mean (SD) weight loss at 12 months in pounds was 13.7 (15.) (range: -85 to +20) for sibutramine plus WMP and 5 (13.2) (range: -79 to +20) for the WMP only (\( P<0.001 \)). The percentage change in weight was -6% (6.7) and -2.2% (5.5) for the drug and nondrug groups, respectively (\( P<0.001 \)). Figure 4 shows that 80.9% of the subjects randomized to only the structured WMP had less than a 5% weight loss, as compared with 52.7% for those randomly
Cost-Effectiveness of Sibutramine in the LOSE Weight Study: Evaluating the Role of Pharmacologic Weight-Loss Therapy Within a Weight Management Program

ASSIGNED to sibutramine plus WMP. In contrast, 19.6% of the subjects receiving sibutramine had a weight loss ≥10%, compared with 10% of those receiving only the WMP.

Table 2 displays the health care utilization and corresponding cost for enrolled subjects 12 months before study enrollment. There were significant differences between the 2 groups with respect to all physician visits and obesity-related physician visits. Persons randomly assigned to the sibutramine group had more physician visits (median = 10) than the nondrug group (median = 8). The only significant difference with respect to costs was that persons in the sibutramine group had higher obesity-related physician visit costs (median=$166.46) than did those in the nondrug arm (median = $82.42), (P<0.001).

Table 3 displays the health care utilization for the 12-month period after enrollment in the study. This utilization reflects all health care received after study enrollment, regardless of whether the subject had follow-up visits for the study. The major differences in utilization between the 2 groups after enrollment were a higher number of obesity-related physician visits, total prescriptions, and obesity-related prescriptions in the sibutramine-plus-WMP group as compared with the WMP-only group. Health care costs were also significantly greater for the sibutramine-plus-WMP group compared with the WMP-only group with respect to obesity-related physician visits, total prescriptions, obesity-related prescriptions, total health care expenditures, and obesity-related health care expenditures. Because these comparisons reflect differences between the groups without controlling for baseline differences, it may not be appropriate to attempt to interpret these findings. Rather, the primary analysis focused on the magnitude of change from 12 months before enrollment to 12 months after enrollment.

The change in medical resource consumption and expenditures from before-study to after-study enrollment is shown in Table 4. There were no differences in overall health care resources used between the groups in outpatient visits (P = 0.80), hospitalizations (P = 0.45), or professional service claims (P = 0.70) over time. The sibutramine-plus-WMP group had more prescription medications than the WMP-only group (P<0.001). The median change in the number of prescriptions was 9 for the sibutramine-plus-WMP group compared with the WMP-only group: a median of $1,279 for those receiving sibutramine compared with $271 for those in the nondrug group (P<0.001).

As noted above, an expert panel rated medical resource use into 1 of 3 categories with respect to whether it was obesity-related. Table 4 displays the change in medical resources for

### Table 1 Demographics of the Sibutramine and Nondrug Groups

<table>
<thead>
<tr>
<th>Item</th>
<th>Sibutramine Group (n = 281)</th>
<th>Nondrug Group (n = 220)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD (years)</td>
<td>47.2 ± 10.7</td>
<td>49.6 ± 10.4</td>
<td>0.01*</td>
</tr>
<tr>
<td>Age, range (years)</td>
<td>19-79</td>
<td>23-72</td>
<td></td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>21</td>
<td>15</td>
<td>0.09†</td>
</tr>
<tr>
<td>Weight, mean ± SD (lbs)</td>
<td>283.3 ± 49.9</td>
<td>227.8 ± 40.8</td>
<td>0.01†</td>
</tr>
<tr>
<td>BMI, mean ± SD (kg/m²)</td>
<td>38.6 ± 7.0</td>
<td>36.8 ± 5.6</td>
<td>0.01*</td>
</tr>
<tr>
<td>BMI, range (kg/m²)</td>
<td>30.0-68.6</td>
<td>27.9-56.8</td>
<td></td>
</tr>
<tr>
<td>Body fat, mean ± SD (%)</td>
<td>40.7 ± 6.1</td>
<td>39.8 ± 6.0</td>
<td>0.10*</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>109.7 ± 17.3</td>
<td>106.4 ± 14.0</td>
<td>0.03*</td>
</tr>
<tr>
<td>Chronic disease score, mean ± SD ($)</td>
<td>$929 ± $1,040</td>
<td>$1,154 ± $1,108</td>
<td>0.02‡</td>
</tr>
</tbody>
</table>

* Wilcoxon rank sum test. † Chi square. ‡ Student t test.
BMI = body mass index.
obesity-related goods and services from the year before the study to 12 months after study enrollment. Again, resource use was similar between the 2 groups except for prescription medications and change in total expenditures. The median change in the number of obesity-related prescriptions was 3 for the sibutramine-plus-WMP group, compared with 0 for the WMP-only group ($<0.001). The group receiving sibutramine plus WMP also had a higher change in total expenditures than did the WMP-only group ($<0.001). Obesity-related costs represented 32% ($408/$1,279) of all health care expenditures for the sibutramine-plus-WMP group versus 11% ($31/$271) for the WMP-only group, over this time frame.

The a priori cost-effectiveness analysis specified that obesity-related costs were to be used in the primary analysis. The denominator for the cost-effectiveness analysis was either weight loss (in pounds) or percentage change in weight. The average weight loss and percentage weight loss are shown in Table 5. The average cost-effectiveness of sibutramine plus WMP was $32 for each pound of weight loss. For the WMP-only group, the average cost-effectiveness was $12 for each pound of weight loss. The incremental cost-effectiveness ratio (ICER) was $44 per additional pound of weight loss (95% confidence interval [CI], $42-$46). When median costs and weight-loss values were used, the ICER was $42 per additional pound of weight loss. When the cost-effectiveness analysis was conducted using percentage change in weight, the ICER for sibutramine plus WMP was $101 per each additional percentage change in weight loss (95% CI, $99-$102).

A sensitivity analysis was conducted using total costs instead of obesity-related costs only. The ICER for sibutramine plus WMP was $194 (95% CI, $188-$200) per additional pound of weight loss when using mean values for cost and weight. For the additional percentage change in body weight, the ICER was $399 (95% CI, $391-$406) when total costs were used. When the costs of sibutramine were excluded, the mean obesity-related total costs were $19 (SD $721) for the drug and $54 (SD $582) for the nondrug groups, respectively (data not shown in tables). In this situation, sibutramine plus the WMP was the dominant strategy, with lower costs and a greater effect. A sensitivity analysis that increased the cost of clinic visits by 50% had a negligible effect, changing the ICER from $44 to $45 per pound of weight loss.

In a multivariate analysis (Table 6), the strongest predictor of total health care costs was the study arm, with those subjects receiving sibutramine plus WMP having an estimated annual cost of $474 more than subjects not receiving sibutramine ($<0.001). Interaction terms were evaluated in the model but were not significant.

Discussion

The results of this study suggest that the cost-effectiveness of sibutramine plus a structured WMP was approximately $44 per additional pound of weight loss as compared with the structured WMP alone. For this cohort of subjects, obesity-related costs represented a modest proportion of their total health care expenditures, 32% ($408/$1,279) for the sibutramine-plus-WMP group versus 11% ($31/$271) for the WMP-only group. When all health care costs were included, the incremental cost-effectiveness of sibutramine plus WMP was $194 per additional pound ($423 per additional kilogram) of weight loss. This analysis examines weight loss over a 1-year period, but the benefits of weight loss are likely to extend beyond such a time period. Although a recent systematic review documents the clinical effectiveness of sibutramine,27 long-term studies of sibutramine (5 years or more) are needed to estimate the extended cost-effectiveness.

The results of this study may be generalizable to other settings where a WMP exists and patients are responsible for paying for part of their antiobesity medications. In this analysis, we use a nonparametric bootstrap approach to estimate the cost-effectiveness and corresponding CIs. The method we used resampled the original data 1,000 times, in essence repeating the study 1,000 times. This allows us to obtain 95% CIs for the study. Therefore, although the trial was just 1 study, we have, in effect, used a very large study (more than 200 subjects in each arm) to simulate the cost-effectiveness 1,000 times.

Other pharmacological therapies for weight loss exist, but few economic studies have been conducted evaluating them. Bharmal et al. evaluated the cost-effectiveness of sibutramine and orlistat with a decision model using data from reported clinical trials.28 In their analysis, presented as a poster abstract, the cost-
The efficacy of orlistat was $531 per kilogram of weight loss versus $303 per kilogram of weight loss for sibutramine.

Recently, Warren and colleagues examined the incremental cost utility of sibutramine compared with diet and lifestyle advice for treatment of obesity. In this analysis, the cost-effectiveness of sibutramine was estimated using a decision model that accounted for obesity-related cardiovascular disease and diabetes. The incremental cost per quality-adjusted life-year (QALY) for sibutramine was $9,299.

Two health technology assessment reports commissioned by the United Kingdom's National Health Service evaluated sibutramine and orlistat independently. These studies reported the incremental cost per QALY of sibutramine was £10,000 (approximately $18,700 in 2005) and £45,881 (approximately $85,750) for orlistat. There are no firm standards for an "acceptable" cost-effectiveness ratio, but many analysts reference $50,000 per QALY or less as an acceptable threshold in the United States.

Other studies have also found relationships between obesity and increased medical care costs. Most relevant to this study, Raebel et al. compared the participants in the LOSE Weight study with a matched control group of nonobese persons (BMI 18.5 to 24.9). That analysis found that obese persons had a greater number of hospitalizations, prescription medications, professional claims, and outpatient visits than nonobese persons. The median annual cost was significantly different between the groups: $585 for obese persons and $333 for nonobese persons. Thompson et al. found that, in comparison with persons with a BMI of 20-24.9 kg/m², costs for persons with a BMI of 25-29.9 kg/m² and ≥ 30 kg/m² were significantly higher for prescription drugs and for all types of medical care. Narbro et al. evaluated both the types and costs of medications more often taken by obese individuals via a cross-sectional comparison of the use of prescription medications in 1,286 obese individuals in the Swedish Obese Subjects (SOS) study and 958 reference individuals. Compared with nonobese persons, obese individuals had more medications for cardiovascular disease, pain, diabetes, and asthma. The overall cost of medications for obese individuals was more than 50% higher than for the nonobese population.

A retrospective database analysis of patients completing a membership health survey at Kaiser Permanente in northern California also demonstrated increased health care resource utilization and costs among obese members. Total health care costs were increased in patients with a BMI of 30-34.9 kg/m² and > 35 kg/m². Mean annual costs were 25% greater among those with BMI of 30-34.9 kg/m² and 44% higher among those with BMI ≥ 35 kg/m² compared with those with BMI of 20-24.9 kg/m² (P=0.003). More recently, Daviglus et al. found
that higher BMI values in young and middle-age persons was significantly associated with higher Medicare expenditures once these persons were older.41 Average annual charges for nonoverweight (BMI 18.5-24.9) women were $6,367 as compared with $11,985 for severely obese (BMI ≥ 35) women, with cumulative expenses being $76,866 and $174,752, respectively. Another analysis of health care costs among the civilian noninstitutionalized population found that persons with a BMI between 18.5 and 24.9 had mean annual expenditures of $2,970 compared with $4,333 for persons with a BMI ≥ 30.42

The decision to include antiobesity medications as a covered benefit by managed care organizations is a difficult one. Many ask to what extent the health plan is responsible for eating and other lifestyle habits of its members. However, it is clear that the long-term consequences of obesity are substantial in terms of morbidity, mortality, and health care costs. Managed care organizations must balance the up-front cost of technologies with the likelihood that downstream costs will be borne by another entity or the government. Currently, Medicare does not provide reimbursement for obesity treatments, but a press release from the Centers for Medicare and Medicaid Services indicates that obesity treatments may be covered in the future.43 Coverage for obesity treatments in the United States by managed care organizations is inconsistent, with few organizations having clear clinical strategies for addressing weight management.44 A survey of HMOs found that 38.7% of plans covered prescriptions for anorexiants in 2003.45 In comparison, 50.9% of HMOs covered smoking cessation aids.

The study presented here evaluated sibutramine in the context of a structured WMP. The WMP portion of the study gave subjects the option of attending 2 of 20 American Heart Association seminars offered on weight management. In addition, participants were required to meet at least twice with a prevention specialist. The structured WMP offered as a part of this study is consistent with the notion that drug therapy alone is insufficient to produce significant weight loss. Payers willing to cover some or all of the cost of weight-loss drugs should do so with coverage contingent upon participation in behavioral therapy in a WMP.

There are several strengths to the analysis presented here. First, unlike most economic analyses of obesity treatments, our cost-effectiveness study was based solely upon clinical trial data. We did not model the lifetime cost-effectiveness. Other studies extrapolate short-term weight loss into long-term changes in risk for comorbid conditions associated with obesity. This approach to extrapolation is tenuous because there has been only 1 study verifying these assumptions.46 Second, our study included the full range of obese individuals, including subjects who were older than 65 years (6%) and also subjects with BMIs

### TABLE 3 Health Care Utilization and Costs for the 12-Month Period After Study Enrollment

<table>
<thead>
<tr>
<th>Utilization</th>
<th>Sibutramine Group (n = 281)</th>
<th>Nondrug Group (n = 220)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All physician visits</td>
<td>Median (5th, 95th percentile)</td>
<td>Median (5th, 95th percentile)</td>
<td>0.003</td>
</tr>
<tr>
<td>Obesity-related physician visits</td>
<td>8 (2, 19)</td>
<td>7 (3, 19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All hospital visits</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0.54</td>
</tr>
<tr>
<td>Obesity-related hospital visits</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Professional service claims</td>
<td>1 (0, 16)</td>
<td>1 (0, 15)</td>
<td>0.76</td>
</tr>
<tr>
<td>Obesity-related professional service claims</td>
<td>0 (0, 1)</td>
<td>0 (0, 1)</td>
<td>0.74</td>
</tr>
<tr>
<td>Prescriptions obtained (new and refills)</td>
<td>20 (4, 65)</td>
<td>17 (0.5, 58)</td>
<td>0.002</td>
</tr>
<tr>
<td>Obesity-related prescriptions</td>
<td>5 (1, 20)</td>
<td>0 (0, 15)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Costs                                      | $406.05 (90.82, 1,176.68)         | $353.22 (90.82, 1,205.93)     | 0.09     |
| Obesity-related physician costs            | $158.93 (45.41, 412.16)           | $113.52 (22.70, 888.59)       | <0.001   |
| Hospital costs                             | $0.00 (0.00, 0.00)                | $0.00 (0.00, 0.00)            | 0.53     |
| Obesity-related hospital costs             | $0.00 (0.00, 0.00)                | $0.00 (0.00, 0.00)            | N/A      |
| Professional service costs                 | $0.00 (0.00, 2,998.39)            | $0.00 (0.00, 2,939.43)        | 0.76     |
| Obesity-related professional service costs | $0.00 (0.00, 83.53)               | $0.00 (0.00, 61.93)           | 0.75     |
| Prescription medication costs              | $435.12 (0, 4,250.61)             | $715.36 (2.43, 3,768.38)      | <0.001   |
| Obesity-related prescription medication costs| $0.00 (0.00, 873.48)             | $0.00 (0.00, 862.73)          | <0.001   |
| Total health care expenditures             | $1,325.94 (131.85, 13,296.97)     | $1,485.83 (240.35, 11,601.46) | <0.001   |
| Obesity-related total health care expenditures| $207.83 (45.41, 1,217.54)        | $191.05 (45.40, 1,619.89)     | <0.001   |

* All comparisons made using the Wilcoxon rank sum test.
Several limitations should be considered when interpreting the results of our study. This analysis examined health care consumption over a 1-year period. Although the long-term consequences of obesity are costly in terms of medical resources consumed, this study was of insufficient duration to fully capture these consequences. This limitation is evident in the absence of measurable changes in both obesity-related and all health care resource utilization and costs between the preperiod and intervention period (Table 4). Another significant limitation of this study was the ability of randomization to ensure that the groups were equal at baseline. This issue has been discussed in detail elsewhere. Briefly, the nonequivalence of the groups at baseline was related to the higher dropout rate of subjects randomized to receive only structured WMP. This study did not blind subjects to treatments, thus persons wanting the medication to assist in weight loss were more likely to disenroll from the study, creating nonequivalent groups. This difference in baseline values was taken into account in the multivariate analysis, most notably because baseline BMI was an independent predictor.

Another limitation of this study is that among patients randomized to sibutramine, the length of therapy was less than 1 year, an average of 222 days per year (data not presented). We don't know if the cost-effectiveness of therapy would improve or decline if the medication were used the full 365 days, but the majority of benefit obtained from the product appeared to be realized during the first 6 months of treatment.

When classifying medications and resource use as obesity-related or not, we did not attempt to reconcile differences between the reviewers or arrive at a consensus. However, the intraclass correlation coefficients (a measure of level of agreement) ranged from 0.69 to 0.80, depending upon the type of medical service being evaluated. These values represent good to very good agreement among the experts.

This study also examined only the direct costs of obesity from the perspective of a managed care organization. We did not take into account indirect costs, such as absenteeism, loss of productivity, on-the-job injury, and premature mortality. Nonetheless, previous research has documented that, as BMI increases, so do the number of sick days, short-term disability, and other indirect costs. Sturm asserts that, based on data from Health Care for Communities, a national household telephone survey in 1997-1998, the effects of obesity on physical health-related quality of life are similar to 30 years of aging. Sturm further claims that obesity has a stronger association with reduced health-related quality of life and increased health care spending than does either problem drinking or smoking.

Another limitation of this study was the use of national fee schedules for utilization of medical services and average wholesale price for medications. Managed care organizations pay less than average wholesale price for medications, so this study overstated the actual managed care organization drug cost and provides a conservative estimate of the cost-effectiveness of sibutramine. In addition, subjects receiving sibutramine were required to initially pay for the medication and then were reimbursed 75% of the cost to Kaiser Permanente. Previous research has shown that reducing consumer cost sharing may improve weight loss. Thus, the true cost to the health plan was lower than the price used in the calculations. Using contract prices or increasing the amount of consumer cost sharing for sibutramine is likely to improve the cost-effectiveness of this therapy.

### Table 4

<table>
<thead>
<tr>
<th>Item</th>
<th>Sibutramine Group (n = 281)</th>
<th>Nondrug Group (n = 220)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient visits</td>
<td>Median 9th, 95th Percentile</td>
<td>Median 9th, 95th Percentile</td>
<td></td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>1 0, 3 1 0, 3</td>
<td>0 0, 0 0, 0</td>
<td>0.80</td>
</tr>
<tr>
<td>Professional service claims</td>
<td>0 0, 3 0, 2</td>
<td>0 2, 7, 5</td>
<td>0.45</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>9 -5, 35 2 -9, 27, 5</td>
<td>&lt;0.001 0.001</td>
<td></td>
</tr>
<tr>
<td>Total costs ($)</td>
<td>$1.279 $2.399, $131,090</td>
<td>$271 $4,217, $63,840</td>
<td>&lt;0.001 0.001</td>
</tr>
</tbody>
</table>

* Wilcoxon rank sum test.

A negative number indicates less health care resource use in 12 months after enrollment compared with 12 months prior to enrollment.

> 40 (30%). Third, our study protocol did not require additional visits or services that were outside the scope of routine care for persons enrolled in a structured WMP. The interventions were delivered in the normal context of medical care delivery. Thus, our economic analysis did not have to adjust for protocol-induced utilization or atypical care. Finally, because the study was conducted within a single organization, it is likely that all health care utilization was captured, as compared with economic analyses that rely on patient self-report.

### Limitations

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Cost-Effectiveness of Sibutramine in the LOSE Weight Study: Evaluating the Role of Pharmacologic Weight-Loss Therapy Within a Weight Management Program

**TABLE 5** Cost-Effectiveness Analysis of Sibutramine

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Cost ($)</th>
<th>Mean Effect</th>
<th>Cost/Effect*</th>
<th>Incremental Cost-Effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity-related costs/weight loss in pounds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrug group (weight management only)</td>
<td>58</td>
<td>-5.1 pounds</td>
<td>$12/pound lost</td>
<td>$44/additional pound lost ($44-$46)†</td>
</tr>
<tr>
<td>Sibutramine group (sibutramine + weight management)</td>
<td>443</td>
<td>-13.7 pounds</td>
<td>$32/pound lost</td>
<td></td>
</tr>
<tr>
<td>Obesity-related costs/percentage weight loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrug group (weight management only)</td>
<td>58</td>
<td>-2.2%</td>
<td>$27/percent change in body weight</td>
<td>$101/additional percent change in body weight ($99-$102)†</td>
</tr>
<tr>
<td>Sibutramine group (sibutramine + weight management)</td>
<td>443</td>
<td>-6.0%</td>
<td>$74/percent change in body weight</td>
<td></td>
</tr>
<tr>
<td>Total health care costs/weight loss in pounds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrug group (weight management only)</td>
<td>$1,513</td>
<td>-5.1 pounds</td>
<td>$297/pound lost</td>
<td>$194/additional pound lost ($188-$200)†</td>
</tr>
<tr>
<td>Sibutramine group (sibutramine + weight management)</td>
<td>$3,165</td>
<td>-13.7 pounds</td>
<td>$230/pound lost</td>
<td></td>
</tr>
</tbody>
</table>

* May not equal average cost/average effect due to rounding. † 95% confidence interval. CI = confidence interval.

**Conclusion**

The incremental cost-effectiveness of sibutramine plus a structured WMP was $44 per additional pound of weight loss compared with a structured WMP alone. These results were primarily due to the cost of sibutramine and the additional weight loss for those patients randomized to receive sibutramine. There was no observed cost savings in total health care resource use or expenditures in the sibutramine group compared with the nondrug group.

**DISCLOSURES**

Funding for this investigator-initiated study was provided by the Knoll Pharmaceutical Company, now owned by Abbott Laboratories, and was obtained by authors Marsha A. Raebel, Julie A. Porter, Frances A. Lanty, Elizabeth C. Gay, and John A. Merenich. The investigators collaborated with Knoll Pharmaceutical Company in protocol development and study initiation. Abbott Laboratories was given the right to review the manuscript, but the approval of Abbott Laboratories was not required for publication of this manuscript. Merenich had participated in the speaker’s bureau for Knoll Pharmaceutical Company at the time of the study. Raebel, Porter, Lanty, Gay, and the other authors, Daniel C. Malone, Douglas A. Conner, and Erin A. Vogel, declare no financial interest in Abbott Laboratories. All authors disclose no potential bias or conflict of interest relating to this article.

All authors had access to study data, take responsibility for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication. Malone served as principal author of the study. Study concept and design were contributed by Porter, Raebel, Merenich, Lanty, Malone, Gay, and Vogel. Analysis and interpretation of data were contributed by Malone, Raebel, Porter, Lanty, and Conner. Drafting of the manuscript was primarily the work of Malone and Raebel, and its critical revision was the work of all authors. Statistical expertise was contributed by Malone, Raebel, and Conner.

**REFERENCES**

Cost-Effectiveness of Sibutramine in the LOSE Weight Study: Evaluating the Role of Pharmacologic Weight-Loss Therapy Within a Weight Management Program


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