Agency for Healthcare Research and Quality

Evidence Report/Technology Assessment

Number 103

Pharmacological and Surgical Treatment of Obesity

Summary

Introduction

The age-adjusted prevalence of obesity in the United States was 30.5 percent in 1999-2000.[1] Although obtaining a precise estimate of the change in the prevalence of obesity over time is difficult because of changing definitions, nearly all clinical authorities agree that obesity is reaching epidemic proportions.[1-12] In response, pharmacological and surgical treatments for weight loss have become both more numerous and more commonly used. This report reviews the evidence on such treatments in adults, adolescents, and children.

We assess the efficacy and safety of the following medications used for weight loss: sibutramine, orlistat, fluoxetine, phentermine, diethylpropion, bupropion, zonisamide, topiramate, and sertraline. We also assess the efficacy and safety of various types of bariatric surgery for obesity.

Most of the medications discussed work by suppressing the appetite. Orlistat is a lipase inhibitor that aids weight loss by reversibly binding to the active center of the enzyme lipase, preventing the digestion and absorption of some dietary fats.

Surgical procedures result in weight loss by restricting the size of the stomach or by bypassing a portion of the intestines. Restricting the size of the stomach limits the quantity of food a patient can consume at a single meal. Malabsorptive (bypass) procedures decrease the proportion of nutrients that are absorbed from a meal. Gastric banding achieves weight loss by creating gastric restriction. The uppermost portion of the stomach is encircled by a band to create a gastric pouch. Vertical banded gastroplasty (VBG) and other gastroplasty procedures use the strategy of mechanical restriction to cause weight loss. The upper part of the stomach is stapled to create a narrow gastric inlet or pouch that remains connected with the remainder of the stomach. Roux-en-Y Gastric bypass (RYGB) achieves weight loss through a combination of gastric restriction and malabsorption. Reduction of the stomach to a small gastric pouch results in feelings of satiety following even small meals. In addition, because this small pouch is connected to a segment of the jejunum (which is downstream), thus bypassing the duodenum and very proximal small intestine, absorptive function is reduced.

Methods

Each evidence report requested by the Agency for Healthcare Research and Quality (AHRQ) is guided by a Technical Expert Panel (TEP). We invited a distinguished group of scientists and clinicians, including individuals with expertise in obesity, human nutrition, surgery, pediatrics, and pharmacology, to participate in the TEP for this report. TEP members suggested that our assessment of pharmacological agents include FDA-approved weight loss medications and other medications for which reports have begun to appear regarding their use as weight loss agents. The FDA-approved weight loss drugs are phentermine, sibutramine, orlistat, diethylpropion, and mazindol; however, our TEP advised us to ignore mazindol, because it is no longer used. Our TEP instructed us to include only studies with treatment durations of 6 months or longer.

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Evidence-Based Practice

We searched MEDLINE® (which encompasses information from *Index Medicus*, the Index to Dental Literature, and the Cumulative Index to Nursing and Allied Health Literature) and the Cochrane Controlled Clinical Trials Register Database.

To be accepted for our analysis, the study had to be a randomized controlled trial (RCT) or controlled clinical trial (CCT). For the analysis of surgical studies, we broadened these inclusion criteria to encompass cohort studies and case series, since our TEP and a brief scan of the literature suggested that RCTs and CCTs would be few in number. While acknowledging that inferences about efficacy could not be easily made from case series, we did judge that such studies provided useful information in the absence of trial data, and, furthermore, would be useful to assess complications and adverse events of surgery. To avoid reviewing potentially numerous case reports, we set a threshold of 10 or more patients for inclusion in our review.

We abstracted data from the articles onto a specialized form, containing questions about the study design, the number of patients and comorbidities, dosage, adverse events, the types of outcome measures, and the time from intervention until outcome measurement.

The outcome of interest specified by our sponsor was weight loss. However, excess weight is associated with other health outcomes, such as diabetes mellitus, hypertension, sleep apnea, osteoarthrititis, and so on. Because weight loss achieves its health benefits primarily by reducing the incidence or severity of weight-related comorbidities like diabetes, we also endeavored to assess treatments by comparing their efficacy on these outcomes. Very few of the pharmaceutical studies reported these outcomes, making it not feasible to make across-study comparisons addressing the control of comorbidities. We did find surgical studies that made within-study comparisons of the control of comorbidities, and summarize their findings in this report. We also assessed the case series reports of obesity surgery for the control of selected comorbidities and compared these results to those reported in studies containing within-group comparisons.

Of the medications we assessed, three had up-to-date existing meta-analyses (sibutramine, phentermine, and diethylpropion), and others had a sufficient number of new studies to justify a new meta-analysis (orlistat, topiramate, fluoxetine, and bupropion). In order for a trial to be included in analysis, the associated publication(s) had to report on weight loss, one control or placebo group, provide data prior to the crossover point if the trial was a crossover design, and contain sufficient statistical information for the calculation of a mean difference at 6 months and/or 1 year followup as defined below.

We extracted the followup mean weight loss for the control group, the followup mean weight loss for the medication group, and the standard deviation for each group. For studies that included measures for both a 6-month and 1-year followup, we collected those measures separately. If a study did not report a followup mean, or a followup mean could not be calculated from the given data, the study was excluded from analysis. We extracted weight loss as a positive, i.e., greater than zero, quantity. For studies that did not report a standard deviation or for which a standard deviation could not be calculated from the given data, we imputed the standard deviation by using those studies and groups that did report a standard deviation and weighting all groups equally.

We converted all means and standard deviations to kilograms. We then calculated a mean difference for each study, which was the difference between the control group followup mean weight loss and the medication group followup mean weight loss. A negative mean difference indicates that the medication group experienced more weight loss at followup than did the control group. The mean difference is readily interpretable, as it is measured in kilograms.

For the 6-month and 1-year analyses respectively, we conducted a meta-analysis, estimating a pooled random-effects estimate[13] of the overall mean difference and its associated 95 percent confidence interval. The individual trial mean differences are weighted by both within-study variation and between-study variation in this synthesis. We constructed a forest plot and reported the chi-squared test of heterogeneity p-value based on Cochran's Q.[14] We conducted sensitivity analyses on four study dimensions: Jadad quality score, year of publication, completion rate, and dosage. We assessed the possibility of publication bias by evaluating a funnel plot of the trial mean differences for asymmetry, which can result from the nonpublication of small trials with negative results. Because graphical evaluation can be subjective, we also conducted an adjusted rank correlation test[15] and a regression asymmetry test[16] as formal statistical tests for publication bias.

Each trial included in the weight loss analysis was examined to determine whether it reported data on adverse events. We abstracted either the number of events or the number of people, depending on how the trial chose to report events. The majority of trials recorded the number of events, rather than the number of unique people who experienced the event. Each event was counted as if it represented a unique individual. Because a single individual might have experienced more than one event, this assumption may have overestimated the number of people having an adverse event. After abstracting the data, we identified mutually exclusive subgroups of similar events, based on clinical expertise. For example, one subgroup was "gallbladder problems," consisting of all adverse events

concerning this body system. When we subgrouped events, we again treated all observed events as having occurred in unique individuals. For each adverse event subgroup, we report the number of trials that provided data for any event in the subgroup. We also report the total number of individuals in the medication groups in the relevant trials who were observed to have experienced the event and the total number of patients in the medication groups in those trials. We then report the analogous counts for the control groups in the relevant trials.

For subgroups of events that had two or more trials, at least one event in the medication group, and at least one event in the control group, we performed a meta-analysis to estimate the pooled odds ratio and its associated 95 percent confidence interval. For interpretability, for any significant pooled odds ratio greater than one, which indicates the odds of the adverse event associated with medication is larger than the odds associated with being in the control group, we calculated the relative risk and number needed to harm (NNH). We also conducted a power calculation to determine the lowest adverse-event rate that the medication trials we identified had at least 80 percent power to detect.

For the surgery studies, we conducted several analyses. First, we note that some studies (controlled trials) had control groups, whereas others did not (case series [CS]). Depending on the analysis, these two general study types may have been handled differently. For all surgical studies, we extracted the mean weight loss and its standard deviation for each study group, generally defined by surgery procedure, at 12 months post-operative and at the maximum followup time greater than or equal to 36 months as available. For randomized controlled trials that reported a within-study comparison of two procedures of interest, a mean difference was calculated (mean weight loss in procedure "1" group minus mean weight loss in procedure "2" group). A positive mean difference indicates that patients in the procedure 1 group lost more weight on average than patients in the procedure 2 group. A negative mean difference indicates that patients in the procedure 1 group lost less weight on average than patients in the procedure 2 group. These mean differences were pooled using a random effects model and a 95 percent confidence interval was estimated. For all studies, randomized or not, a pooled mean weight loss for each procedure group was estimated using a random effects model and an associated 95 percent confidence interval was constructed.

Data for diabetes, hypertension, sleep apnea, and lipids were also extracted. A crude proportion across studies was calculated for those who resolved or improved (e.g., the number of people who resolved or improved divided by the number of people with the condition at baseline).

For each group in each study, we recorded the number of deaths observed and the total number of patients in the group. If the study self-identified the deaths as "early" or "postoperative" or if it identified the deaths as within 30 days of the surgery, we termed these "early deaths." If the deaths were self-identified as "late" or if they were identified as after 30 days, we termed these "late deaths." If the study was unclear as to the timing of the recorded deaths, we termed these "unclear deaths." If a study did not report data on death for a group, we recorded zero unclear deaths for that group. That is, we imputed zero for missing data, under the assumption that had there been a death, the authors would have reported it. We calculated the crude death rate. That is, we divided the total number of deaths observed by the total number of patients in the relevant study groups. This calculation treats all patients from all studies equally and does not take into account any variation across studies in mortality rates, but given the small number of observed deaths, this statistic is simple and easily interpretable.

Each surgery study (RCT/CCT or CS) was examined to determine whether it reported data on adverse events other than death. The extraction of data for the surgery adverse event analysis was the same as that described above for the medication trials. After abstracting the data, we identified mutually exclusive subgroups of similar events based on clinical expertise. For selected surgery comparisons (one type of surgery versus another type of surgery) for which there were RCT/CCT data available, we estimated a pooled odds ratio and its associated 95 percent confidence interval using exact methods as described above for the medication adverse events meta-analysis. We also report the crude adverse event rate for each RCT/CCT surgery group (total number of affected patients divided by total number of patients at risk). In addition, we report the crude adverse event rate for each surgery group across all studies (RCT/CCT/CS) combined.

Results

A recent meta-analysis on sibutramine efficacy reported a mean difference in weight loss (compared to placebo) of 3.43 kg at 6 months. At 12 months, the difference was 4.45 kg. Treatment with sibutramine was associated with modest increases in heart rate and blood pressure, very small improvements in glycemic control among diabetics, and (based on the longest duration and best quality studies) small improvements in HDL cholesterol and triglycerides.

In our own meta-analysis on orlistat, mean weight loss for orlistat-treated patients, compared to placebo-treated patients, was 2.51 kg at 6 months; at 12 months, it was 2.75 kg. We found an increase in diarrhea, flatulence, and bloating/

abdominal pain/dyspepsia in orlistat-treated patients, compared to placebo, with relative risks of 3.4, 3.1, and 1.5, respectively.

We identified a published review on phentermine and diethylpropion for weight loss. (Our literature review identified no new RCTs of these drugs since publication.) Compared to placebo, subjects treated with phentermine lost on average 3.6 additional kg of weight at 6 months compared to placebo, while subjects treated with diethylpropion lost on average 3.01 kg of weight, but this difference had only borderline statistical significance. This review did not report side effects or adverse event data.

Our own meta-analysis of fluoxetine studies showed a mean weight loss, compared to placebo-treated patients, of 4.74 kg at 6 months and 3.05 kg at 12 months. There was an increase in nervousness/sweating/tremors, nausea/vomiting, fatigue/asthenia/ hypersomnia/somnolence, insomnia, and diarrhea in fluoxetine-treated patients compared to placebo, with relative risks of 6.4, 2.7, 2.4, 2.0, and 1.7, respectively.

We identified three studies of bupropion for weight loss that were suitable for meta-analysis; two studies reported results at 6 months, the other at 12. The pooled result, compared to placebo treated patients, was 2.8 kg. Bupropion causes dry mouth (RR = 2.99) and insomnia.

We identified six studies (all but one available only as abstracts) of topiramate for weight loss that were suitable for meta-analysis. The pooled result at 6 months, compared to placebo-treated patients, was an additional 6.5 percent of pre-treatment weight lost. Parasthesias (RR = 4.9) and taste perversion (RR = 9.2) were the most commonly reported side effects attributable to topiramate.

Our literature search identified one eligible study that assessed the efficacy of the drug zonisamide for weight loss.[17] Patients were followed for 16 weeks in the double-blind portion of the study, with an additional 16-week single blind extension available. The researchers reported that patients in the zonisamide group lost an average of 6.0 percent of baseline body weight, compared to 1.0 percent for placebo patients ($p < .001$).

We identified no direct comparisons of weight loss medications. Our summary of the results for each drug (compared to placebo) does not support a hypothesis that any one drug is more effective than the others.

We identified numerous reports on obesity surgery. Two RCTs of surgery compared to nonsurgical treatment were considered to be of limited relevance because they used surgical procedures that are considered obsolete. An observational study, the Swedish Obese Subjects (SOS) study,[18-25] matched subjects on 18 variables, including gender, age, height, and weight. At 8 years of followup, among 251 surgically treated patients, the average weight loss was 20 kg (or 16 percent of body weight), whereas among 232 medically treated patients, the average weight did not change. We consider this study as providing conclusive evidence of the superiority of surgical treatment for the patients that were enrolled (middle-aged adults with a BMI of about 41 kg/m^2). The strength of this study is the extended duration of followup, documenting sustained weight loss and improved health up to 10 years following treatment. A series of reports from the SOS study support the superiority of obesity surgery compared to medical therapy in ameliorating or preventing the morbidities due to obesity such as hypertension, diabetes, and lipid abnormalities. At 24 months after surgery, among 845 surgically treated patients and 845 matched controls (two-thirds women, average age of 48, average BMI about 41), the incidence of hypertension, diabetes, and lipid abnormalities was markedly lower in the surgically treated patients (adjusted odds ratios of 0.02 to 0.38, depending on condition).[25] At 8 years of followup, the effect of surgery on the reduction in diabetes risk was still dramatic (odds ratio = 0.16), whereas the effect on reduction in risk for hypertension did not persist (odds ratio = 1.01).[19] However, significant decreases in both systolic (8.3 mm Hg) and diastolic (6.7 mm Hg) blood pressure persisted in the small (6 percent) subset of patients who underwent a gastric bypass and lost significantly more weight than the 94 percent of patients who underwent a vertical banded gastroplasty or gastric banding.[18] Additional reports from the SOS study support a substantial benefit of surgery in reducing sleep apnea,[20] symptoms of dyspnea and chest pain,[20] and improving quality of life.[23] The SOS study is the only one we identified that compares the effect on comorbidities between surgically treated patients and a concurrent control group receiving non-surgical treatment.

Weight loss outcomes were reported in a large number of RCTs comparing various surgical procedures and case series of specific surgical procedures. For patients with a BMI between 35-40 kg/m^2, the data strongly support the superiority of surgical therapy, but cannot be considered conclusive yet, in the absence of a study with a concurrent comparison group. These studies support the conclusion that gastric bypass produces superior weight loss compared to gastroplasty procedures. The weight loss reported in surgical studies is an order of magnitude greater than weight loss reported in pharmaceutical or diet studies of obesity (weight losses of 20 to 40 kg at 1 or 2 years in surgical studies versus 2 to 5 kg in pharmaceutical studies), although direct comparisons cannot be made across studies.

There is no clear pattern of differential mortality between the various procedures, and there is no clear pattern in terms of higher or lower early death rates in randomized trials compared with case series. In these reports early mortality following bariatric surgery is less than 1 percent. Existing reports of post-

operative mortality in unselected populations are twice this value (about 2 percent). Adverse events other than mortality are reported with great variability between the studies. None of the comparisons of complications between various surgical procedures show statistically significant differences. The absolute rates of some complications are substantial, although many may be minor in their degree of severity. For example, the proportion of subjects receiving vertical banded gastroplasty who have gastrointestinal complications is 15.2 percent in the RCT/CCT data and 17.8 percent in the case series data, the proportion of subjects receiving RYGB who experience nutritional deficiencies is 26.8 percent in the case series data (many of these nutritional deficiencies were mild); and the proportion of subjects receiving a banding procedure who require re-operation is 7.3 percent in the case series data. The proportion of patients with adverse events or complications may be on the order of 10 percent to 20 percent, although the majority of these may be mild and respond to conservative treatment. The data also support a reduced occurrence of wound and incisional hernia complications in patients treated laparoscopically compared to open procedures; data are insufficient to reach conclusions about differences in other complications.

As part of our literature search and appraisal process, we attempted to identify studies that reported data specific to adolescent and pediatric populations. Too few studies were identified to permit quantitative analysis. We identified three controlled trials of medication that reported data specific to adolescents. One study (in two reports) assessed mazindol, which was not an included drug for this review.[26,27] A second study assessed the use of a caffeine/ephedrine mixture, which was also not an included drug for this review.[28] The other trial studied sibutramine. At six months, subjects treated with the drug lost a mean of 7.8 kg, which was equal to an 8.5 percent reduction in initial BMI, whereas placebo-treated patients had a significantly smaller 3.2 kg weight loss, which was equal to a 5.4 percent reduction in BMI.

There have been a handful of case reports of bariatric surgery in adolescents, which in total report on 172 subjects. These reports document both benefits in terms of weight loss and resolution of complications and harms in terms of complications. There are no studies comparing these benefits and harms to similar patients receiving alternative therapies, such as diet or medication.

Conclusions

Sibutramine, orlistat, phentermine, diethylpropion (probably), bupropion, fluoxetine, and topiramate all promote weight loss when given along with recommendations for diet. Sibutramine and orlistat are the two most studied drugs. The amount of extra weight loss attributable to these medications is modest (less than 5 kg at 1 year), but this amount still may be clinically significant. No evidence indicates that any particular drug promotes more weight loss than another drug. All of these drugs have side effects. The choice of drug may be made on an individual basis, based on tolerance to the expected side effects.

Surgical treatment is more effective than nonsurgical treatment for weight loss and the control of some comorbidities in patients with a body mass index of 40 kg/m^2 or greater. More data are needed to confirm or refute the relative efficacy of surgery for less severely obese persons. Perioperative mortality rates of less than 1 percent have been achieved by some surgeons and surgical centers. The perioperative mortality rates in other settings may be higher. Surgical treatment is associated with a substantial number of complications and adverse events, although most of these are minor.

The existing literature is almost bereft of data regarding either pharmaceutical or surgical treatment of adolescent and pediatric patients. To the extent that existing data on adults are judged to be inapplicable to adolescents or children, new studies will need to be performed.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Southern California–RAND Evidence-based Practice Center, under Contract No. 290-02-0003. It is expected to be available in July 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 103, *Pharmacological and Surgical Treatment of Obesity*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

Suggested Citation

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