0031-6997/07/5902-151–184$20.00
PHARMACOLOGICAL REVIEWS
Vol. 59, No. 2
50441/3199591
Pharmacol Rev 59:151–184, 2007
Printed in U.S.A

Pharmacological Treatment of the Overweight Patient

GEORGE A. BRAY AND FRANK L. GREENWAY

Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, Louisiana

Address correspondence to: Dr. George A. Bray, Pennington Center, 6400 Perkins Road, Baton Rouge, LA 70808. E-mail: brayga@pbrc.edu

This article is available online at http://pharmrev.aspetjournals.org.
doi:10.1124/pr.59.2.2.

I. Introduction

To use medications properly for treatment of the overweight patient, it is important to start with a framework based on the realities associated with this treatment. These are briefly summarized below:

- Overweight is due to an imbalance between energy intake and energy expenditure.
- Drugs can either reduce food intake or increase energy expenditure.
- Drug treatment does not cure the overweight patient.
- The therapeutic armamentarium of physicians is limited to only a few drugs.
- The use of drugs labors under the negative halo of treatment mishaps.
- Drugs do not work when they are not taken; when drugs are stopped weight regain is the expected outcome.
- Weight loss plateaus during continued treatment when compensatory mechanisms come into play to counterbalance the effect of the drug.
- Monotherapy usually produces weight loss in the range of 10% (5% better than placebo).
- Frustration with the failure to continue to lose weight often leads to discontinuation of therapy and then to weight regain with labeling of the drug as a failure.

Physicians have several strategies for confronting the problems of the overweight patient. The physician can counsel the patient that he or she is concerned about the patient's current level of body weight and can initiate treatment if the patient is interested. Alternatively, if a physician feels uncomfortable with addressing overweight in patients, he or she can ignore the problem and hope that the patient will not raise the issue. Or, finally the physician can wait until the complications of excess weight manifest themselves as diabetes, dyslipidemia, hypertension, or other disorders and then institute appropriate therapy for each of these medical problems. With the current high-quality therapies available to treat diabetes mellitus, dyslipidemia, and hypertension, many physicians would prefer this latter strategy.

[1] Abbreviations: DPP, Diabetes Prevention Program; BMI, body mass index; GLP-1, glucagon-like peptide-1; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GI, gastrointestinal; NPY, neuropeptide Y; POMC, proopiomelanocortin; VLCD, very low-calorie diet; FDA, U.S. Food and Drug Administration; PYY, peptide YY; 5-HT, 5-hydroxytryptamine (serotonin); TNP-470, *O*-(chloroacetyl-carbamoyl); L-796568, (*R*)-*N*-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]-phenyl]-4-[4-[4-(trifluoromethyl)-phenyl]thiazol-2-yl]-benzenesulfonamide, dihydrochloride.

However, if medical treatment of the overweight patient were more effective, physicians might prefer to treat the excess weight and thus delay the onset of the problems related to overweight. This strategy was the basis for the long-term Diabetes Prevention Program (DPP)[1] and the Swedish Obese Subjects Study. In the DPP, the onset of new cases of diabetes among individuals with impaired glucose tolerance was reduced 55% during an average follow-up of 3.2 years in the group who lost weight compared with the control group who did not lose weight (Knowler et al., 2002). In the Swedish Obese Subjects Study, the incidence of new cases of diabetes was reduced to zero over 2 years in patients who lost weight and maintained a weight loss of ≥12%, compared with an incidence of 8.5% for new cases of diabetes in those who did not lose weight (Sjostrom et al., 2004). Thus, effective treatment of the overweight patient at risk for diabetes or hypertension can reduce the risk of developing these serious diseases in the future.

One reason most physicians are reluctant to treat overweight patients is that the treatments are limited in number and effectiveness. At the time this article was written, there were only two drugs approved by the U.S. Food and Drug Administration for long-term use. As monotherapy, these agents can produce an overall weight loss of 8 to 10% among patients who continue to take the medication for >6 months. However, to achieve the elimination of new cases of diabetes as noted above, the weight loss needs to exceed 12%, a goal that is not usually achieved with current monotherapy. Thus, there is a great need for new drugs to be used as monotherapy and probably in combinations when prevention fails.

Both physicians and patients know that overweight is a stigmatized disease (Puhl and Brownell, 2003). One commonly held view is that overweight people are lazy and weak-willed. If fat people just had willpower, they would push themselves away from the table and not be overweight. This widely held view is shared by the public and by health professionals alike. The clamoring of women to be lean and well proportioned supports this view. The declining relative weight of centerfold models in *Playboy* magazine and of women who are winners of the Miss America contest in the latter part of the 20th century also supports this view. Many physicians just do not like to see overweight patients come into their offices. This attitude poses a major challenge to any efforts to improve the lot of people who are overweight.

There can be both medical and cosmetic (self-image) benefits to weight loss. However, they do not necessarily occur together. For example, a 10% weight loss, which would be clinically significant for a 300-pound (145-kg) person, would only reduce body weight by 30 to 270 pounds, a weight change that many people might not notice and would not be considered a cosmetic success. At the other extreme, a 10% weight loss for an individual weighing 150 pounds would lower his or her weight to 135 pounds, which would have a very positive impact on self-image. We also know that cosmetically significant weight losses may not produce clinically significant effects. After liposuction that removed ~7% of body weight, there were no improvements in health-related risk factors. These distinctions are shown in Table 1.

Three other issues aggravate the problem of treating overweight patients. The first is the "negative halo" that surrounds the use of appetite suppressants because amphetamine is addictive. There was never any evidence that dexfenfluramine was addictive. Nonetheless, the drug was scheduled by the U.S. Drug Enforcement Agency as a Schedule IV drug because, on paper, it had chemical similarities to amphetamine.

The second issue is the concern about the plateau of body weight that is reached when homeostatic mechanisms in the body come into play and stop further weight loss. There is an analogy with treatment of hypertension. When an antihypertensive drug is given, blood pressure drops and then stops falling within a few weeks to reach a plateau at a new lower level. The antihypertensive drug has not lost its effect when the plateau occurs, but its effect is being counteracted by physiological mechanisms designed to maintain blood pressure. In the treatment of overweight patients, a similar plateau in body weight is often viewed as a therapeutic failure for the weight loss drug. This is particularly so when weight is regained after the drug is stopped. These attitudes and biases need to change before any effective new therapy will become widely accepted.

The final issue is the toxicity associated with many antiobesity drugs. The disaster that occurred for some of the patients who took the combination of fenfluramine and phentermine is one example (others are listed in Table 2). Aortic regurgitation occurred in up to 25% of the patients treated with this combination of drugs and led many physicians to say, "I told you so" and "I'm certainly glad I didn't use those drugs." This issue has largely subsided with time, but there will always remain a residue of concern among some physicians and among regulators about the potential problems that might sur-

TABLE 1
Cosmetically significant versus clinically significant weight loss

Type of Procedure	Weight Loss	Clinically Significant	Cosmetically Significant
Diet/exercise	10%; from 300 to 270 lb	Yes	No
	10%; from 200 to 180 lb	Yes	Probably not
	10%; from 150 to 135 lb	Yes	Yes
Liposuction	7%; from 220 to 200 lb	No	Probably not
	7%; from 160 to 149 lb	No	Yes
Surgery (gastric bypass)	40%; from 264 to 165 lb	Yes	Yes

TABLE 2
Unintended consequences of some treatments for obesity

Year	Drug	Consequence
1893	Thyroid	Hyperthyroidism
1932	Dinitrophenol	Cataracts/neuropathy
1937	Amphetamine	Addiction
1968	Rainbow pills	Deaths: arrhythmias
1985	Gelatin diets	Cardiac deaths
1997	Phentermine/fenfluramine	Valvulopathy
1998	Phenylpropanolamine	Strokes
2003	Ma huang	Heart attacks/strokes

face when new treatments for overweight are made available to the public. Although the drug treatment of overweight patients has at least a century-long history (Colman, 2005), progress in drug discovery was given a new impetus by the discovery of leptin in 1994 (Zhang et al., 1994). This peptide demonstrated that overweight can be caused by a hormone deficiency and be reversed by replacement of that hormone (Halaas et al., 1995; Maffei et al., 1995; Farooqi et al., 2002). Even before the discovery of leptin, overweight had been declared to be a chronic disease by a National Institutes of Health Consensus Conference in 1985 (Bray, 2004). In the 20th century, bad eating habits were considered a primary cause for overweight. Because some bad habits can be behaviorally extinguished over a 12-week period of time, overweight medications approved before 1985 were approved for periods up to 12 weeks as an adjunct to a lifestyle change program. Equating overweight with bad habits and the stigmatization of obesity slowed the use of overweight medications chronically, as is done with medications for other chronic diseases (Puhl and Brownell, 2003). With the recognition that longer-term therapy was needed, clinical trials have been extended in length. Since 1990, only three medications have been approved for the chronic treatment of overweight, and one of them, dexfenfluramine, was withdrawn 2 years later (Anonymous, 1996).

II. Using the Currently Available Drugs

In this article, we review the field of drug therapy for the overweight patient. Table 3 lists the drugs that are available and whether they are approved for long-term use by the U.S. Food and Drug Administration or are restricted (scheduled) by the U.S. Drug Enforcement Agency on the basis of the belief that there is risk of abuse from the drug. For individuals desiring more detail or additional guidance in the use of medications to treat overweight, information can be found in a variety of sources (Bray and Greenway, 1999; National Heart, Lung, and Blood Institute and North American Association for the Study of Obesity, 2000; Haddock et al., 2002; Yanovski and Yanovski, 2002; Kim et al., 2003; Padwal et al., 2004, 2005; Colman, 2005; Li et al., 2005; Snow et al., 2005; Vettor et al., 2005).

As a guide for the use of medications, we will use an algorithm that was described by the National Heart, Lung, and Blood Institute. The first step in this algorithm is to measure height, weight, and waist circumference to establish the body mass index (BMI) and the degree of central adiposity. If the BMI, ([weight in kilograms divided by the square of the height in meters] or [weight in pounds divided by square of the height (inches)] $\times$ 703] is >30 kg/m^2 the patient is by definition obese and can be considered for medications. Overweight individuals with a BMI between 27 and 30 kg/m^2 may also be considered if they have diabetes, hypertension, sleep apnea, or another medical condition that would benefit from weight loss.

Waist circumference is also an important indicator of risk from excess fat. The currently recommended upper limit for waist circumference in the United States is 102 cm (40 inches) for a man and 88 cm (35 inches) for a woman. A recent proposal from the International Diabetes Federation requires the presence of central adiposity to diagnose the metabolic syndrome and uses values for waist circumference >80 cm for females and >94 cm for males. Another important initial step in evaluating the overweight patient is to assess associated (comorbid) conditions by measuring blood pressure, glucose, lipids and, when indicated, by performing other tests. With results from this laboratory panel and waist circumference, the metabolic syndrome can be diagnosed. This is best done with the criteria from the National Cholesterol Education Panel Adult Treatment III Guidelines (Table 4).

Once the patient has been established as an appropriate candidate to lose weight and he or she is motivated to do so, the next step is to set a weight loss goal. Most patients have an unrealistic view of how much weight they can lose. For them, a weight loss of $<15\%$ is often viewed as a failure. In contrast, weight loss using monotherapy with the drugs that are currently available is not usually $>10\%$. It is, thus, important for physician and patient alike to set a weight loss goal for initial therapy that is not $>10\%$ and to set a lower limit for weight loss of $<5\%$, which will suggest that an alternative strategy is needed.

The next step is to be certain that the patient is "ready" to lose weight. With use of ideas from psychology, the patient must be ready to work on weight loss as opposed to not yet thinking about the problem. Once the weight goal is established and patients are prepared to take charge of their weight loss program, the next steps are to help them develop lifestyle changes that will benefit their program. The most important of these is monitoring what they eat, where they eat it, and under what circumstances they eat. A second element is to provide advice on diet and physical activity. Replacing voluntary choices with "portion-controlled" choices at one or more meals can be helpful. There are frozen foods, ready-to-make food items, and canned meal replacements that can be used for this purpose. Patients also need more exercise. One strategy is to have them get a step-counter and record the number of steps they take with the goal of

TABLE 3
Drugs producing weight loss that are approved by the U.S. Food and Drug Administration

Drug Name	Trade Name(s)	Dosage	U.S. Drug Enforcement Agency Schedule	Side Effects and Comments
Cannabinoid receptor antagonist				
Rimonabant	Accomplia	20 mg/day	N.A.	Depressive symptoms, nausea, diarrhea; approved by the Center for Proprietary Medicinal Products in Europe—approval by FDA pending
Pancreatic lipase inhibitor				
Orlistat	Xenical	120 mg t.i.d. before meals	None	Daily vitamin pill in the evening; may interact with cyclosporine
Norepinephrine-serotonin reuptake inhibitor				
Sibutramine	Meridia Reductil	5–15 mg/day	IV	Raises blood pressure slightly; do not use with monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, sumatriptan, dihydroergotamine, meperidine, methadone, pentazocine, fentanyl, lithium, or tryptophan
Sympathomimetic drugs				
Diethylpropion	Tenuate Tepanil Tenuate Dospan	25 mg t.i.d. 25 mg t.i.d. 75 mg in A.M.	IV	All sympathomimetic drugs are similar; do not use with monoamine oxidase inhibitors, guanethidine, alcohol, sibutramine, or tricyclic antidepressants
Phentermine	Standard release: Adipex-P, Fastin, Obenix, Oby-Cap, Oby-Trim, Zantryl	18.75–37.5 mg t.i.d.	IV	
	Slow release: Ionamin	15–30 mg/day in A.M.		
Benzphetamine	Didrex	25–50 mg 1–3 times/day	III	All sympathomimetic drugs are similar; do not use with monoamine oxidase inhibitors, guanethidine, alcohol, sibutramine, or tricyclic antidepressants
Phendimetrazine	Standard release: Bontril PDM, Plegine, X-Trozine	35 mg t.i.d. before meals	III	All sympathomimetic drugs are similar; do not use with monoamine oxidase inhibitors, guanethidine, alcohol, sibutramine, or tricyclic antidepressants
	Slow release: Bontril, Prelu-2, X-Trozine	105 mg/day in A.M.		

TABLE 4
The National Cholesterol Education Program Adult Treatment Panel III and the International Diabetes Federation criteria for diagnosis of the metabolic syndrome

Criterion	ATP-III Modified Criteria		International Diabetes Federation	
Waist circumference				
Female	>35 inches	>88 cm	≥31 inches	≥80 cm
Male	>40 inches	>102 cm	≥37 inches	≥94 cm
HDL cholesterol				
Female	<50 mg/dl	<1.29 mmol/l	<50 mg/dl	<1.29 mmol/l
Male	<40 mg/dl	<1.03 mmol/l	<40 mg/dl	<1.03 mmol/l
Glucose	≥110 mg/dl	≥6.2 mmol/l	≥100 mg/dl	≥5.6 mmol/l
Blood pressure	≥130/85 mm Hg		≥130/85 mm Hg	

gradually increasing this number to 10,000 steps/day. In a review of lifestyle treatment used with pharmacotherapy in randomized clinical trials Poston et al. (2001) found that balanced-deficit diets were used in 40.7%, low-calorie diets in 25% and self-monitoring behavioral strategies in 23.1% of patients (Poston et al., 2001). When a patient returns to you, establish whether he or she has met the goals. If so, the patient continues as is, but if after 3 months he or she fails to meet the goals, then medications may be considered. The next step is to discuss the pros and cons of medication with the patient. An algorithm from the American College of Physicians (Snow et al., 2005) recommends six medications: orlistat, sibutramine,

phentermine, diethylpropion, fluoxetine, and bupropion. The first four have been approved by the U.S. Food and Drug Administration for treatment of overweight patients, but fluoxetine and bupropion have not, and they should not be used primarily for this purpose. In our view, fluoxetine and bupropion should only be used for weight loss in special situations. Fluoxetine is appropriate for the overweight patient who is depressed. Bupropion may also be helpful in reducing or preventing weight gain when people try to stop smoking and when they are depressed.

III. Drugs Approved by the U.S. Food and Drug Administration or the European Medicinal Evaluation Agency for Treatment of Overweight Patients

A. Drugs Approved for Long-Term Use

1. Orlistat.

a. Mechanism of action. Orlistat is a lipase inhibitor. In pharmacological studies, it was shown to be a potent selective inhibitor of pancreatic lipase and to thus reduce the intestinal digestion of fat. The drug has a dose-dependent effect on fecal fat loss, increasing it to ~30%. Thus, orlistat is recommended to be used with a diet that has 30% of its energy as fat. Orlistat has little effect in subjects eating a low-fat diet, as might be anticipated from its mechanism of action. In single-dose randomized and placebo-controlled studies, 120 mg of orlistat was shown to increase glucagon-like peptide-1 (GLP-1) and C-peptide more than placebo (Damci et al., 2004), to increase fecal fat loss but decrease the acute increase in cholecystokinin (O'Donovan et al., 2003), but not to influence the behavioral measures of satiety (Goedecke et al., 2003).

b. Long-term studies. Results of a number of 1- to 2-year long-term clinical trials with orlistat have been published. The results of a 2-year trial are shown in Fig. 1 (Sjostrom et al., 1998). The trial consisted of two parts. In the 1st year, patients received a hypocaloric diet calculated to be 500 kcal/day less than the patient's requirements. During the 2nd year, the diet was calculated to maintain body weight. By the end of year 1, the placebo-treated patients lost −6.1% of their initial body weight and the drug-treated patients lost −10.2%. The patients were randomized again at the end of year 1. Those switched from orlistat to placebo gained weight from −10 to −6% below baseline. Those switched from placebo to orlistat lost weight from −6 to −8.1% below baseline, which was essentially identical to the −7.9% weight loss in the patients treated with orlistat for the full 2 years.

In a second 2-year study, 892 patients were randomized to orlistat or placebo (Davidson et al., 1999). One group received placebo throughout the 2 years (97 patients), and a second group received orlistat (120 mg three times per day) for 2 years (109 patients). At the end of 1 year, the dose for two-thirds of the group treated with orlistat for 1 year was changed to 60 mg three times per day (102 patients), and the others were switched to placebo (95 patients) (Davidson et al., 1999). After 1 year, the weight loss was −8.67 kg in the orlistat-treated group and −5.81 kg in the placebo group ($P < 0.001$). During the 2nd year, those switched to placebo after 1 year reached the same weight as those treated with placebo for 2 years (−4.5% in those treated with placebo for 2 years and −4.2% in those switched to placebo during year 2).

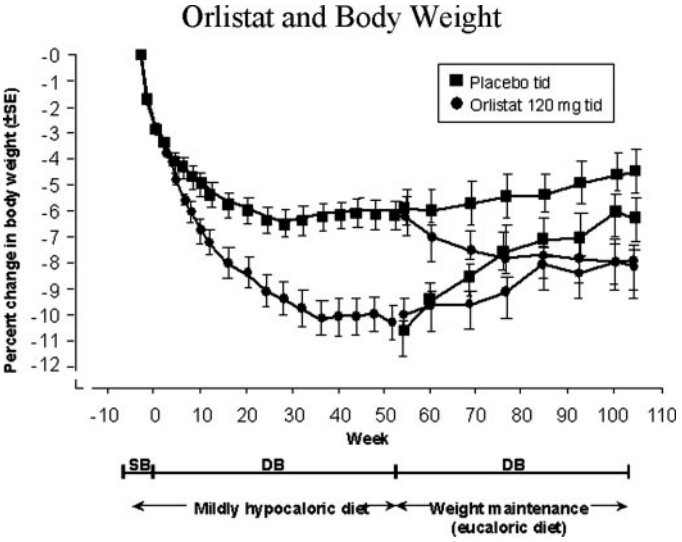

FIG. 1. Double-blind, randomized clinical trial of orlistat versus placebo with a rerandomization of participants after the 1st year. Reprinted from *The Lancet*, vol. 352, Sjostrom et al., "Randomized Placebo-Controlled Trial of Orlistat for Weight Loss and Prevention of Weight Regain in Obese Patients: European Multicenter Orlistat Study Group," pp 167–172, copyright 1998, with permission from Elsevier.

In a third 2-year study, 783 patients remained in the placebo or orlistat-treated groups at 60 or 120 mg three times per day for the entire 2 years (Rossner et al., 2000). After 1 year with a weight-loss diet, the placebo group lost −7 kg, which was significantly less than the −9.6 kg lost by the group treated with orlistat 60 mg three times daily or the −9.8 kg lost by the group treated with 120 mg of orlistat three times daily. During the 2nd year, when the diet was liberalized to a "weight maintenance" diet, all three groups regained some weight. At the end of 2 years, the patients in the placebo group were −4.3 kg below baseline, the patients treated with 60 mg of orlistat three times per day were −6.8 kg below baseline, and the patients who took 120 mg of orlistat three times per day were −7.6 kg below baseline.

The final 2-year trial evaluated 796 subjects in a general-practice setting (Hauptman, 2000). After 1 year of treatment with 120 mg of orlistat three times per day, the orlistat-treated patients ($n = 117$) lost −8.8 kg, compared with −4.3 kg in the placebo group ($n = 91$). During the 2nd year, when the diet was liberalized to "maintain body weight," both groups regained some weight. At the end of 2 years, the orlistat group was −5.2 kg below their baseline weight

compared with −1.5 kg below baseline for the group treated with placebo.

The pooled 2-year data from these four studies are shown in Fig. 2. This figure contains information on both the 120- and 60-mg-three-times-a-day doses. It is clear that there is a dose response. The maximal weight loss was achieved between 6 and 9 months, and then there was a slow regain in all of the groups during the rest of the study.

The results of a 4-year double-blind, randomized, placebo-controlled trial with orlistat have also been reported (Torgerson et al., 2004). A total of 3304 overweight patients, 21% of whom had impaired glucose tolerance, were included in this Swedish trial (Fig. 3). The lowest body weight was achieved during the 1st year: >−11% below baseline in the orlistat-treated group and 6% below baseline in the placebo-treated group. Over the remaining 3 years of the trial, there was a small regain in weight, such that by the end of 4 years, the orlistat-treated patients were −6.9% below baseline compared with −4.1% for those receiving placebo. The trial also showed a 37% reduction in the conversion of patients from impaired glucose tolerance to diabetes; essentially all of this benefit occurred in the patients with impaired glucose tolerance when they were enrolled into the trial.

Weight maintenance with orlistat was evaluated in a 1-year study (Hill et al., 1999). Patients were enrolled if they had lost >8% of their body weight over 6 months while eating a 1000 kcal/day (4180 kJ/day) diet. The 729 patients were randomized to receive placebo or orlistat at 30, 60, or 120 mg three times per day for 12 months. At the end of this time, the placebo-treated patients regained 56% of their body weight, compared with 32.4% in the group treated with 120 mg of orlistat three times per day. The other two doses of orlistat were no different from placebo in preventing the regain of weight.

c. Studies in special populations.

i. Diabetic patients. Patients with diabetes treated with orlistat, 120 mg three times daily for 1 year, lost more weight than the placebo-treated group (Hollander et al., 1998; Kelley et al., 2002; Miles et al., 2002). The subjects with diabetes also showed a significantly greater decrease in hemoglobin A_{1c} levels. In another study of orlistat and weight loss, investigators pooled data on 675 subjects from three of the 2-year studies described previously in which glucose tolerance tests were available (Heymsfield et al., 2000). During treatment, 6.6% of the patients taking orlistat converted from a normal to an impaired glucose tolerance test, compared with 10.8% in the placebo-treated group. None of the orlistat-treated patients who originally had normal glucose tolerance developed diabetes, compared with 1.2% in the placebo-treated group. Of those who initially had normal glucose tolerance, 7.6% in the placebo group but only 3% in the orlistat-treated group developed diabetes.

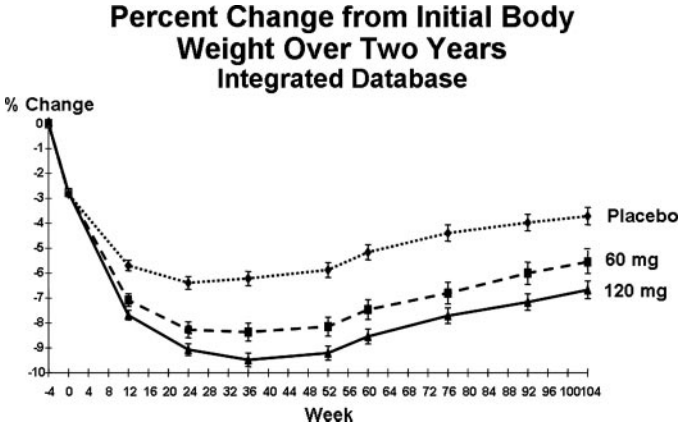

FIG. 2. Two-year pooled data comparing orlistat and 120 and 60 mg three times a day and placebo. From Hoffmann-LaRoche data, with permission from Dr. Jonathan Hauptman.

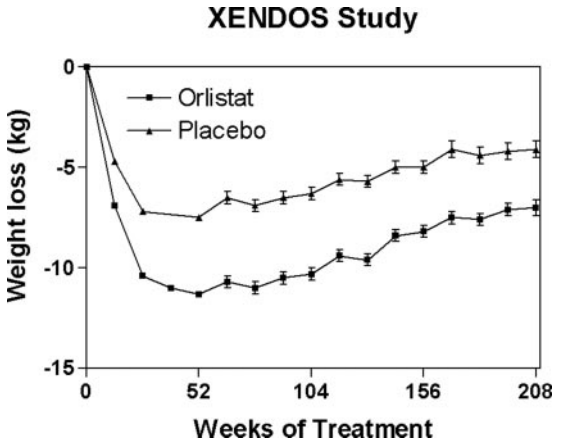

FIG. 3. Effect of orlistat on body weight in a 4-year randomized, placebo-controlled clinical trial.

The effect of orlistat in preventing diabetes has been assessed in a 4-year study (Torgerson et al., 2004). In this trial weight was reduced by 2.8 kg (95% CI 1.1–4.5 kg) compared with placebo, and the conversion rate to diabetes was reduced from 9 to 6% for a relative risk reduction of 0.63 (95% CI 0.46–0.86) (Padwal et al., 2005).

ii. Metabolic syndrome and lipids. In a further analysis, patients who participated in the studies described above were divided into the highest and lowest quintiles for triglycerides and HDL cholesterol levels (Reaven et al., 2001). Those with high triglyceride and low HDL cholesterol levels were labeled "syndrome X," and those with the lowest triglyceride levels and highest HDL cholesterol levels were the "nonsyndrome X" controls. With this classification, there were almost no men in the nonsyndrome X group, compared with an equal sex breakdown in the syndrome X group. In addition, the syndrome X group had slightly higher systolic and diastolic blood pressure levels and a nearly 2-fold higher level of fasting insulin. Besides weight loss, the only difference between the placebo and orlistat-treated patients was the decrease in LDL cholesterol levels in the

patients treated with orlistat. However, the syndrome X subgroup showed a significantly greater decrease in triglyceride and insulin levels than those without syndrome X. Levels of HDL cholesterol increased more in the syndrome X group, but LDL cholesterol levels showed a smaller decrease than that in the nonsyndrome X group. All of the clinical studies with orlistat have shown significant decreases in serum cholesterol and LDL cholesterol levels that usually are greater than decreases that can be accounted for by weight loss alone (Bray and Greenway, 1999). One study showed that orlistat reduces the absorption of cholesterol from the GI tract, thus providing a mechanism for the clinical observations (Mittendorfer et al., 2001).

iii. Studies in children. A multicenter trial tested the effect of orlistat in 539 obese adolescents (Chanoine et al., 2005). Subjects were randomized to placebo or 120 mg of orlistat three times a day and a mildly hypocaloric diet containing 30% fat. By the end of the study BMI decreased -0.55 kg/m^2 in the drug-treated group but increased $+0.31$ kg/m^2 in the placebo group. By the end of the study, weight increased by only $+0.51$ kg in the orlistat-treated group, compared with $+3.14$ kg in the placebo-treated group (Fig. 4). This difference was due to differences in body fat. The side effects were gastrointestinal in origin, as expected from the mode of action of orlistat. A second small 6-month randomized clinical trial from a single site failed to show a difference resulting from treatment with orlistat in a population of 40 adolescents (Maahs et al., 2006).

d. Meta-analysis of orlistat studies. Several meta-analyses of orlistat have been published (Haddock et al., 2002; Avenell et al., 2004; Li et al., 2005). By pooling six studies Haddock et al. (2002) estimated the weight loss in patients treated with orlistat to be -7.1 kg (range -4.0 to -10.3 kg) compared with -5.02 kg (range -3.0 to -6.1 kg) for the placebo-treated groups. In the meta-analysis of Li et al. (2005), the overall mean difference between orlistat and placebo after 12 months of therapy in 22 studies was -2.70 kg (95% CI -3.79 to -1.61 kg). Because this analysis included diabetic and nondiabetic subjects, we have summarized the data from the five 2-year studies in Table 5.

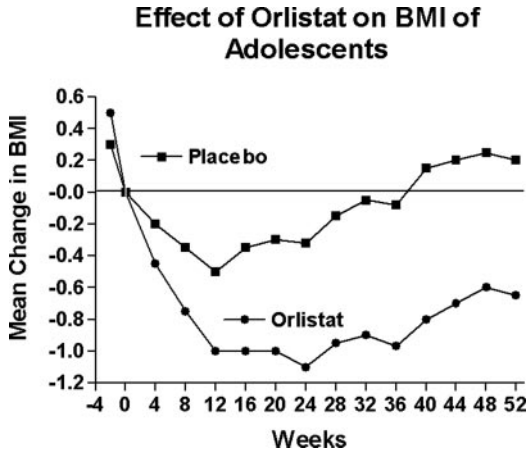

FIG. 4. Effect of orlistat on body mass index in a randomized, placebo-controlled clinical trial of orlistat in adolescents. Reproduced from *The Journal of the American Medical Association*, volume 293, pp 2873–2883. Copyright © 2005 American Medical Association.

In another meta-analysis of orlistat, 8-year-long studies, only one of which was in diabetic subjects, examined the effects of weight loss at 1 and 2 years and on the various laboratory and clinical responses. The overall effect of orlistat on weight loss at 12 months using the weighted mean difference was -3.01 kg (95% CI -3.48 to -2.54 kg) (Table 6). After 24 months, the overall effect of orlistat on weight loss was -3.26 kg (95% CI -4.15 to -2.37 kg). In terms of weight maintenance, the overall effect of orlistat after 12 months was -0.85 kg (95% CI -1.50 to -0.19 kg) (Davidson et al., 1999; Hill et al., 1999; Hauptman, 2000; Rossner et al., 2000). The pooled data show significant overall effects after 1 year of treatment on the change in cholesterol [-0.34 mM (95% CI -0.41 to -0.027)] ($n = 7$ studies), the change in LDL cholesterol [-0.29 mM (95% CI -0.34 to -0.24)] ($n = 7$ studies), the change in HDL cholesterol [-0.03 mM (95% CI -0.05 to -0.01)] ($n = 6$ studies), the change in triglycerides [0.03 mM (95% CI -0.04 to 0.10)] ($n = 6$ studies), the change in hemoglobin A1c [-0.17% (95% CI -0.24 to -0.10] ($n = 3$ studies) (Hollander et al., 1998; Lindgarde, 2000; Broom et al., 2002), the change in systolic blood pressure [-2.02 mm Hg (95% CI -2.87 to -1.17)] ($n = 7$ studies), and the change in diastolic blood pressure [-1.64 mm Hg (95% CI -2.20 to -1.09)] ($n = 7$ studies)]. In a meta-analysis focused on the use of orlistat in diabetics Norris et al. (2004) reported a weighted mean difference in favor of orlistat of -2.6 kg (95% CI -3.2 to -2.1) after 52 to 57 weeks of treatment.

e. Safety considerations. Orlistat is not absorbed to any significant degree from the gastrointestinal tract, and its side effects are thus related to the blockade of triglyceride digestion in the intestine (Zhi et al., 1999). Fecal fat loss and related GI symptoms are common initially, but they subside as patients learn to use the drug (Bray and Greenway, 1999). The quality of life in patients treated with orlistat may improve despite concerns about GI symptoms. Orlistat can cause small but significant decreases in fat-soluble vitamins. Levels usually remain within the normal range, but a few patients may need vitamin supplementation. Because it is impossible to tell which patients need vitamins, it is wise to

TABLE 5
Meta-analysis of studies with long-term use of orlistat
Adapted from Li et al. (2005).

Reference	Mean
	95% CI
Davidson et al. (1999)	-2.95 (-4.45 to -1.45)
Hauptman (2000)	-3.80 (-5.37 to -2.23)
Rossner et al. (2000)	-3.00 (-4.17 to -1.83)
Sjostrom et al. (1998)	-4.20 (-5.26 to -3.14)
Torgerson et al. (2004)	-4.17 (-4.60 to -3.74)

TABLE 6
Meta-analysis of the studies using orlistat

Adapted from Avenell et al. (2004).

Reference	Treatment		Placebo		Weight	Weighted Mean Difference
	n	Mean ± S.D.	*n*	Mean ± S.D.		
					%	*95% CI*
Sjostrom et al. (1998)	343	−8.10 ± 8.21	340	−3.90 ± 7.02	11.1	−4.20 (−5.35 to −3.05)
Hollander et al. (1998)	156	−3.84 ± 5.00	151	−1.43 ± 5.10	11.4	−2.41 (−3.54 to −1.29)
Davidson et al. (1999)	657	−8.76 ± 9.48	223	−5.81 ± 10.01	6.5	−2.95 (−4.45 to −1.45)
Rossner et al. (2000)	241	−8.13 ± 8.22	236	−5.23 ± 7.40	7.4	−2.90 (−4.30 to −1.50)
Hauptman (2000)	210	−5.40 ± 7.44	212	−1.41 ± 6.31	8.4	−3.99 (−5.31 to −2.67)
Lindegarde (2000)	190	−4.20 ± 7.03	186	−2.90 ± 6.74	7.5	−1.30 (−2.69 to 0.09)
Finer et al. (2000)	110	−3.29 ± 6.85	108	−1.31 ± 6.29	4.8	−1.98 (−3.73 to −0.23)
Broom et al. (2002)	259	−5.80 ± 8.50	163	−2.30 ± 6.40	8.7	−3.50 (−4.79 to −2.21)

provide a multivitamin routinely with instructions to take it before bedtime. Orlistat does not seem to affect the absorption of other drugs, except cyclosporin.

2. Sibutramine.

a. Mechanism of action. Sibutramine is a highly selective inhibitor for the reuptake at nerve endings of norepinephrine and serotonin and, to a lesser degree, dopamine. In preclinical experimental and clinical studies, it reduced food intake. In a double-blind placebo-controlled 2-week trial, a 30-mg/day dose of sibutramine reduced food intake by 23% on day 7 and 26% on day 14 relative to placebo and also decreased the percentage of fat eaten. A smaller dose of 10 mg also significantly reduced food intake at 14 days (Rolls et al., 1998). The effect of sibutramine on food intake has also been examined over a longer period of time (Barkeling et al., 2003). The first 2 weeks of this 10-month trial were conducted in a double-blind, randomized, placebo-controlled, crossover design. Participants then entered a 10-month open-label trial with repeat food intake at the end. There was a 16% reduction in energy intake at the test lunch in the first part of the study (after 2 weeks). Ten months later, there was still a 27% reduction compared with participants' preweight loss placebo-treatment food intake. In animals, sibutramine also stimulates thermogenesis, but there are conflicting data in humans (Hansen et al., 1998; Seagle et al., 1998). Mechanistic studies have shown that the effect of sibutramine can be mimicked by combining a selective serotonin reuptake inhibitor (fluoxetine) with a selective norepinephrine reuptake inhibitor (nisoxetine). When injected alone these specific reuptake inhibitors do not replicate the reduction of food intake produced by sibutramine (Jackson et al., 1997). Sibutramine treatment of experimental animals increased the activity of the sympathetic nervous system and attenuated the rise in NPY and fall in POMC in the arcuate nucleus in energy-restricted rats indicating that this drug influences both monoamine and peptidergic pathways involved in food intake (Levin and Dunn-Meynell, 2000).

b. Long-term studies. Sibutramine has been approved by the U.S. Food and Drug Administration for long-term use in the treatment of overweight patients. Sibutramine has been evaluated extensively in several multicenter trials lasting 6 to 24 months. In a 6-month dose-ranging study of 1047 patients, 67% treated with sibutramine achieved a 5% weight loss from baseline, and 35% lost ≥10% (Bray and Greenway, 1999). There was a clear dose-response effect in this 24-week trial, and patients regained weight when the drug was stopped, indicating that the drug remained effective when used. Data from this multicenter trial are shown in Fig. 5 (Bray et al., 1999). In a 1-year trial of 456 patients who received sibutramine (10 or 15 mg/day) or placebo, 56% of those who stayed in the trial for 12 months lost at least 5% of their initial body weight, and 30% of the patients lost 10% of their initial body weight while taking the 10-mg dose (Smith and Goulder, 2001).

Three trials have assessed the value of using sibutramine to prevent regain of body weight (Apfelbaum et al., 1999; James et al., 2000; Mathus-Vliegen, 2005). In a multicenter trial, participants were initially given a very low-calorie diet (VLCD) for 6 weeks to induce weight loss (Apfelbaum et al., 1999). Of the initial 181 subjects enrolled, 142 were randomized to either 10 mg/day of sibutramine or placebo after losing −6 kg or more with the VLCD. After another 12 months, those receiving the

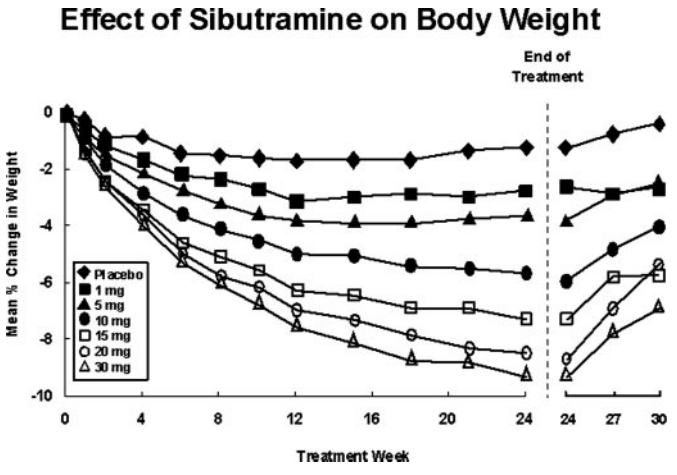

FIG. 5. Six-month randomized, placebo-controlled dose-ranging trial with sibutramine at six doses and placebo. Reproduced from Bray et al. (1999) with permission.

drug lost an additional 6.4 kg compared with a small weight gain of +0.2 kg for those receiving placebo. The authors concluded that sibutramine had effectively enhanced the initial weight loss and maintained it for an additional 12 months.

This was followed by the Sibutramine Trial of Obesity Reduction and Maintenance (STORM) Trial that lasted 2 years and provided evidence for weight maintenance (James et al., 2000) (Fig. 6). Seven centers participated in this study, in which patients were initially enrolled in an open-label phase and treated with 10 mg/day of sibutramine for 6 months. Of the patients who lost >8 kg, two-thirds were then randomized to sibutramine and one-third to placebo. During the 18-month double-blind phase of this trial, the placebo-treated patients steadily regained weight, maintaining only 20% of their weight loss at the end of the trial. In contrast, the subjects treated with sibutramine maintained their weight for 12 months and then regained an average of only 2 kg, thus maintaining 80% of their initial weight loss after 2 years (James et al., 2000). Despite the higher weight loss with sibutramine at the end of the 18 months of controlled observation, the blood pressure levels of the sibutramine-treated patients were still higher than those of the patients treated with placebo.

The final trial for weight maintenance with sibutramine was a study conducted at eight hospitals in the Netherlands in which patients were initially treated before referral to their primary care physicians. A total of 221 patients began the VLCD. Of these patients, 189 lost the required ≥10 kg during 3 months and were randomized to 10 mg/day of sibutramine or placebo for the remaining 15 months. Mean weight loss during the VLCD period for the successful subjects was 14.5% from baseline. After 2 additional months of treatment in the hospital clinic, the final 13 months were conducted in the general practitioner's offices. At 18 months, the odds ratio was 1.76 (95% CI 1.06–2.93) favoring weight loss with sibutramine ($P = 0.03$). With use of the intent-to-treat analysis, >80% of the weight loss at the end of the VLCD was maintained by 70, 51, and 30% of those receiving sibutramine at 6, 12, and 18 months compared with 48, 31, and 20% of those receiving placebo, and these differences were significant at all time points ($P \leq 0.03$) (Mathus-Vliegen, 2005).

The possibility of using sibutramine as intermittent therapy has been tested in a randomized, placebo-controlled trial lasting 52 weeks (Wirth and Krause, 2001) (Fig. 7). The patients randomized to sibutramine received one of two regimens. One group received continuous treatment with 15 mg/day for 1 year, and the other group had two 6-week periods when sibutramine was withdrawn. During the periods when the drug was replaced by placebo, there was a small regain in weight that was lost when the drug was resumed. At the end of the trial, the continuous-therapy and intermittent-therapy groups lost the same amount of weight.

c. Studies in special populations.

i. Diabetic patients. The effects of sibutramine in diabetic patients have been examined in eight studies. In a 3-month (12-week) trial, patients with diabetes who were treated with 15 mg/day of sibutramine lost 2.4 kg (2.8%), compared with a loss of 0.1 kg (0.12%) in the placebo group (Finer et al., 2000). In this study, hemoglobin A_{1c} levels decreased 0.3% in the drug-treated group and remained stable in the placebo group. Fasting glucose values decreased 0.3 mg/dl in the drug-treated patients and increased 1.4 mg/dl in the placebo-treated group. In a 24-week trial, the dose of sibutramine was increased from 5 to 20 mg/day over 6 weeks (Fujioka et al., 2000). Among those who completed the treatment, weight loss was −4.3 kg (4.3%) in the sibutramine-treated patients, compared with −0.3 kg (0.3%) in placebo-treated patients. Hemoglobin A_{1c} levels decreased 1.67% in the drug-treated group, compared with 0.53% in the placebo-treated group. These changes in glucose

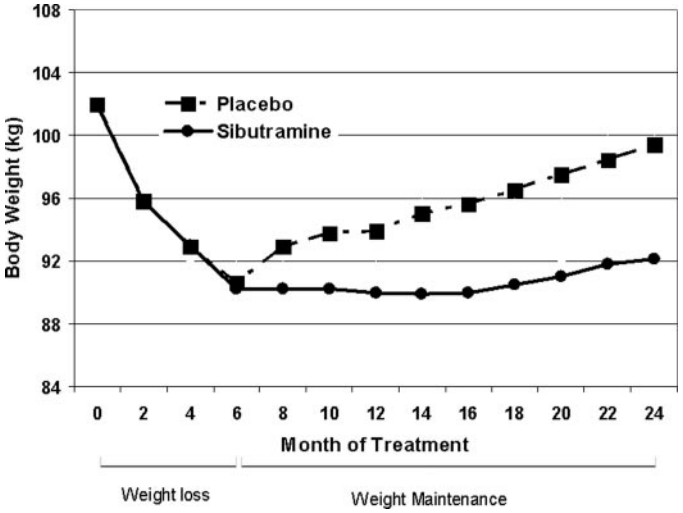

FIG. 6. Effect of sibutramine on weight maintenance. Adapted from James et al. (2000).

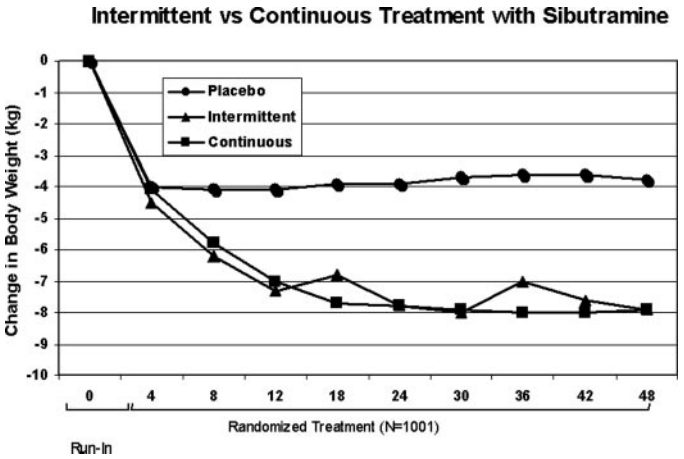

FIG. 7. Effect on body weight of continuous versus intermittent use of sibutramine in a randomized, placebo-controlled clinical trial. Adapted from *The Journal of the American Medical Association*, volume 286, pp 1331–1339. Copyright © 2001 American Medical Association.

and hemoglobin A_{1c} levels were expected from the amount of weight loss associated with drug treatment.

In a 12-month multicenter, randomized, placebo-controlled study (McNulty et al., 2003), 194 diabetics receiving metformin were assigned to placebo ($n = 64$), 15 mg/day of sibutramine ($n = 68$), or 20 mg/day of sibutramine ($n = 62$). At 12 months, weight loss in the 15 mg/day group was 5.5 ± 0.6 kg and in the 20 mg/day group it was 8.0 ± 0.9 kg compared with 0.2 ± 0.5 kg in the placebo group. Glycemic control improved in parallel with weight loss. Sibutramine raised sitting diastolic blood pressure by >5 mm Hg in 43% of those receiving 15 mg/day of sibutramine compared with 25% for the placebo group ($P < 0.05$). Pulse rate increased >10 beats/min in 42% of those receiving sibutramine, compared with 17% for those receiving placebo.

The 2-year trial by Redmon et al. (2005) was a double-blind, randomized, placebo-controlled trial that had a crossover for the control group after the 1st year. The treatment group received 10 mg/day of sibutramine for the entire 2 years. In addition, they had a portion-controlled diet used for 7 days at the end of each 2 months. There was a significantly greater weight loss in the drug-treated group that reached −9.7 kg at 12 months, compared with −1.6 kg in the placebo-treated group. During the 2nd year, those receiving sibutramine continuously regained weight slowly, rising to a maximal loss of −6.3 kg at 24 months. In contrast, the group that got sibutramine only during the 2nd year weighed less at 24 months than those receiving sibutramine continuously for 2 years (−6.3 kg in the continuous treatment group versus −9.7 kg for the crossover group). There was an improvement in diabetic control associated with the weight loss.

A meta-analysis has been done of eight studies in diabetic patients receiving sibutramine (Vettor et al., 2005). In this meta-analysis, the changes in body weight, waist circumference, glucose, hemoglobin A_{1c}, triglycerides, and HDL cholesterol favored sibutramine. The mean weight loss was 5.53 ± 2.2 kg for those treated with sibutramine and 0.90 ± 0.17 kg for the placebo-treated patients. There was no significant change in systolic blood pressure, but diastolic blood pressure was significantly higher in the sibutramine-treated patients (Vettor et al., 2005). In the meta-analysis by Norris et al. (2004) the net weight loss over 12 to 26 weeks in 4 trials, including 391 diabetic patients, was 4.5 kg (95% CI 7.2–1.8 kg).

ii. Hypertensive patients. Some trials have reported the use of sibutramine to treat overweight patients with hypertension. In a 3-month trial, where all patients received β-blockers, with or without thiazides, for their hypertension McMahon et al. (2000) reported that sibutramine-treated patients lost 4.2 kg (4.5%), compared with a loss of 0.3 kg (0.3%) in the placebo-treated group. Mean supine and standing diastolic and systolic blood pressure levels were not significantly different between drug-treated and placebo-treated patients. Heart rate, however, increased by 5.6 ± 8.25 beats/min (mean ± S.D.) in the sibutramine-treated patients, compared with an increase of 2.2 ± 6.43 beats/min in the placebo group. In another 52-week trial, patients with hypertension whose blood pressure levels were controlled with calcium channel blockers with or without β-blockers or thiazides (McMahon et al., 2000) received sibutramine in doses that were increased from 5 to 20 mg/day during the first 6 weeks. Weight loss was significantly greater in the sibutramine-treated patients, averaging −4.4 kg (4.7%), compared with −0.5 kg (0.7%) in the placebo-treated group. Diastolic blood pressure levels decreased 1.3 mm Hg in the placebo-treated group and increased +2 mm Hg in the sibutramine-treated group. Systolic blood pressure levels increased +1.5 mm Hg in the placebo-treated group and +2.7 mm Hg in the sibutramine-treated group. Heart rate was unchanged in the placebo-treated patients, but increased by +4.9 beats/min in the sibutramine-treated patients.

The effects of sibutramine on blood pressure have been evaluated in a meta-analysis of 21 studies by Kim et al. (2003). Sibutramine produced a significant overall weight loss and a significant increase in both systolic and diastolic blood pressures. In a subgroup analysis, they found the effect on systolic blood pressure to be greater with higher doses of sibutramine, in individuals weighing ≥92 kg and in younger individuals (<44 years of age). Older individuals with body weights of ≥92 kg also showed a greater rise in diastolic blood pressure. In another analysis of two studies with use of sibutramine for 48 weeks Jordan et al. (2005) reported that sibutramine significantly reduced body weight but did not lead to a difference in systolic blood pressure after 48 weeks (−0.1 ± 15.5 mm Hg for placebo versus −0.2 ± 1.52 mm Hg for the sibutramine group). However, the change in diastolic blood pressure was statistically significant with a small rise of +0.3 ± 9.5 mm Hg in the sibutramine group and a decrease of −0.8 ± 9.2 mm Hg in the placebo group ($P = 0.049$).

iii. Sibutramine plus behavioral weight loss. Sibutramine has been studied as part of a behavioral weight-loss program in two reports (Wadden et al., 2005). With sibutramine alone, the weight loss over 12 months was ~5.0 ± 7.4 kg (5%). Behavior modification alone produced a weight loss of 6.7 ± 7.9 kg. Adding a brief behavioral therapy session to a group that also received sibutramine produced a slightly larger weight loss of 7.5 ± 8.0 kg. When the intensive lifestyle intervention was combined with sibutramine, the weight loss increased to 12.1 ± 9.8 kg. When a structured meal plan was added to the medication and behavioral modification in one of these studies (Wadden et al., 2005), the weight loss increased further to 15 kg (Wadden et al., 2001). Completing the food intake records was a strong predictor of success (Wadden et al., 2005). Those in the combined therapy group receiving an intensive lifestyle program and sibutramine who were in the highest third for record keeping lost 18.1 ± 9.8 kg compared with 7.7 ± 7.5 kg in the lowest third for record-keeping (Fig. 8).

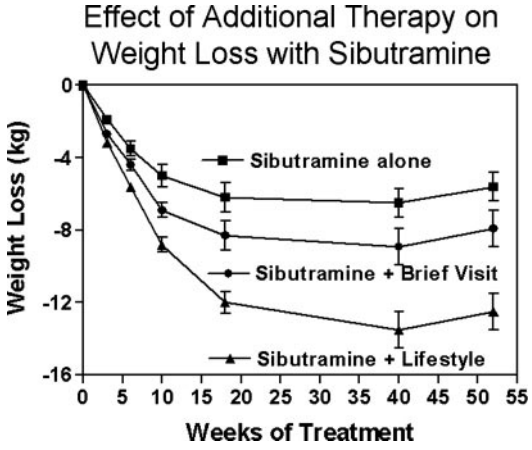

FIG. 8. Effect on body weight loss of sibutramine alone or with additional supplementary behavior therapies. The study had four groups. Lifestyle was essentially the same as sibutramine + brief visit and was left off. Combined therapy was sibutramine + lifestyle 30 group visits. Data from Wadden et al. (2005).

iv. Studies in children. Sibutramine has also been used in children and adolescents (Berkowitz et al., 2003, 2006; Godoy-Matos et al., 2005). In a single center, 85 adolescents aged 13 to 17 years with a BMI of 32 to 44 kg/m^2 were randomized to treatment for 6 months with placebo or sibutramine. Weight loss in the drug-treated group was 7.8 kg, for an 8.5% reduction in BMI, compared with 3.2 kg in the placebo group, for a 4.0% reduction in BMI. When the placebo group was switched to sibutramine after 6 months, there was an additional significant weight loss in this group. In a 12-month, multicenter, randomized, placebo-controlled trial, 498 adolescents aged 12 to 16 were treated with sibutramine or placebo (Berkowitz et al., 2006). The dose of sibutramine was 10 mg/day for 6 months and then increased to 15 mg/day in those who had not lost >10% of their baseline BMI. After 12 months, the mean absolute change in BMI was −2.9 kg/m^2 (−8.2%) in the sibutramine group compared with −0.3 kg/m^2 (−0.8%) in the placebo group ($P < 0.001$). Triglycerides HDL cholesterol, and insulin sensitivity improved, and there was no significant difference in either systolic or diastolic blood pressure.

d. Meta-analysis of sibutramine studies. Several meta-analyses of sibutramine have been published (Haddock et al., 2002; Avenell et al., 2004; Li et al., 2005). By pooling four studies Haddock et al. (2002) estimated the weight loss in patients treated with sibutramine as −5.3 kg (range 4.0–7.3 kg) compared with −1.8 kg (range 0.8–3.3 kg) for the placebo-treated groups. In the meta-analysis of Li et al. (2005), the overall mean difference after 12 months of therapy in five studies was −4.45 kg (95% CI −5.29 to −3.62 kg) (Table 7).

In the meta-analysis by Avenell et al. (2004), the overall placebo-subtracted effect of sibutramine at 12 months was −4.12 kg (95% CI −4.97 to −3.26 kg). Table 8 shows a summary for each of the trials that had data for sibutramine out to 12 months (Avenell et al., 2004). After an additional interval in the weight maintenance studies, the data showed a loss at 15 months of −3.70 kg (95% CI −5.71 to −1.69 kg) (Apfelbaum et al., 1999) and at 18 months of −3.40 kg (95% CI −4.45 to −2.35 kg) (James et al., 2000).

e. Combining sibutramine and orlistat. Because sibutramine works on noradrenergic and serotonergic reuptake mechanisms in the brain and orlistat works peripherally to reduce triglyceride digestion in the GI tract, their mechanisms of action do not overlap and combining them might provide additive weight loss (Wadden et al., 2000). To test this possibility, researchers randomly assigned patients to orlistat or placebo after 1 year of treatment with sibutramine (Wadden et al., 2000). During the additional 4 months of treatment, the two groups lost no significant amount of weight and adding orlistat had no detectable effect.

In an open-label randomized 12-week study, 86 overweight patients were assigned to treatment with 120 mg of orlistat three times a day, to treatment with 10 mg/day of sibutramine, the combination of orlistat and sibutramine, or to a diet group. During the 12 weeks, sibutramine produced more weight loss than orlistat alone. In another study, 150 obese subjects were randomized to 850 mg of metformin b.i.d., 120 mg of orlistat t.i.d., or 10 mg of sibutramine b.i.d. treatment for 6 months. The BMI decreased by −9.1, −9.9, and −13.6%, respectively. Weight loss was greater in the sibutramine group than in either the metformin or orlistat groups ($P < 0.001$) (Gokcel et al., 2002). A third study, also of 6 months' duration, randomized 89 obese women to orlistat, sibutramine, or the combination and showed weight losses of 5.5, 10.1, and 10.8 kg, respectively. The combination was superior to orlistat but not to sibutramine alone (Sari et al., 2004). A fourth study randomized 86 obese subjects to 10 mg/day of sibutramine, 360 mg/day of orlistat, the combination, or diet alone. In this study, the combination group lost more weight than the diet alone or orlistat groups, but the amount lost was similar to that for sibutramine alone (Aydin et al., 2004). Thus, adding orlistat to sibutramine did not significantly enhance weight loss, confirming the observations of Wadden et al. (2000) and Kaya et al. (2004).

TABLE 7
Meta-analysis of net weight loss with sibutramine (placebo-drug)
Adapted from Li et al. (2005).

Reference	Mean
	95% CI
Apfelbaum et al. (1999)	−5.70 (−7.77 to −3.63)
Smith and Goulder (2001)	−3.00 (−4.55 to −1.45)
Hauner et al. (2000)	−5.30 (−6.83 to −3.77)
McNulty et al. (2003)	−4.80 (−6.02 to −3.58)
Wirth and Krause (2001)	−4.00 (−5.01 to −2.99)

TABLE 8
Meta-analysis of the effect of sibutramine versus placebo and diet at 12 months
Adapted from Avenell et al. (2004).

Reference	Treatment		Control		Weight	Weighted Mean Difference
	n	Mean ± S.D.	*n*	Mean ± S.D.		
					%	*95% CI*
Apfelbaum et al. (1999)	81	−5.20 ± 7.50	78	0.50 ± 5.70	17.14	−5.70 (−7.77 to −3.63)
McMahon et al. (2000)	142	−4.40 ± 7.16	69	−0.50 ± 6.06	21.32	−3.90 (−5.75 to −2.05)
Smith and Goulder (2001)	154	−4.40 ± 7.16	157	−1.60 ± 6.37	32.20	−2.80 (−4.31 to −1.29)
Smith and Goulder (2001)	153	−6.40 ± 7.73	157	−1.60 ± 6.37	29.34	−4.32 (−6.38 to −3.22)

f. Dosage and safety considerations. Sibutramine is available in 5-, 10-, and 15-mg doses; 10 mg per day as a single dose is the recommended starting level, with titration up or down, depending on response. Doses higher than 15 mg/day are not recommended. Of the patients who lost 2 kg (4 lb) in the first 4 weeks of treatment, 60% achieved a weight loss of >5%, compared with <10% of those who did not lose 2 kg (4 lb) in 4 weeks. Combining data from the 11 studies on sibutramine showed a reduction in triglyceride, total cholesterol, and LDL cholesterol levels and an increase in HDL cholesterol levels that were related to the magnitude of the weight loss.

3. Rimonabant.

a. Mechanism of action. There are two cannabinoid receptors CB-1 (470 amino acids in length) and CB-2 (360 amino acids in length). The CB-1 receptor has almost all the amino acids that comprise the CB-2 receptor with additional amino acids at both ends. CB-1 receptors are distributed through the brain in the areas related to feeding, on fat cells, in the gastrointestinal tract. The CB-2 receptors are primarily on immune cells.

Marijuana and tetrahydrocannabinol, which stimulate the CB-1 receptor, both increase high fat and high sweet food intake. There are two well-characterized endogenous endocannabinoids called anandamide and 2-arachidonylglycerol. When injected into the brain, they also increase food intake. In human beings, fasting increases the levels of these endocannabanoids. The rewarding properties of cannabinoid agonists are mediated through the mesolimbic dopaminergic system.

Rimonabant is a specific antagonist of the CB-1 receptor. It inhibits intake of sweet foods by marmosets and reduces intake of high-fat foods in rats. Intake of standard rat chow is not affected by rimonabant. In addition to inhibiting the intake of highly palatable foods, pair-feeding experiments in diet-induced obese rats showed that the rimonabant-treated animals lost 21% of their body weight compared with 14% in the pair-fed controls. This suggests, at least in rodents, that rimonabant increases energy expenditure in addition to reducing food intake. CB-1 knockout mice are lean and resistant to diet-induced weight gain. CB-1 receptors are up-regulated on adipocytes in diet-induced obese mice, and rimonabant increases adiponectin, a fat cell hormone associated with insulin sensitivity (Bensaid et al., 2003; Kirkham, 2005; Juan-Pico et al., 2006; Pagotto et al., 2006).

b. Long-term studies. The results of four phase III trials of rimonabant for the treatment of overweight have been published. The first trial, called the Rimonabant in Obesity (RIO)-Europe trial, was reported in 2005 (Van Gaal et al., 2005) and was intended to be conducted in Europe, but slow recruitment led to inclusion of 276 subjects from the United States. This was a 2-year trial with 1-year results reported in this article. A total of 1507 patients with a BMI >30 kg/m^2 without comorbidities or a BMI >27 kg/m^2 with hypertension or dyslipidemia were stratified on whether they lost > or <2 kg during the run-in and then were randomized in a ratio of 1:2:2 to receive placebo, 5 mg/day of rimonabant, or 20 mg/day of rimonabant. The energy content of the diet was calculated by subtracting 600 kcal/day from the energy requirements calculated from the Harris-Benedict equation. The trial consisted of a 4-week run-in period followed by 52 weeks of drug treatment. Of those who started, 61% (920) completed the 1st year. Weight loss was −2% in the placebo group and −8.5% in the 20-mg rimonabant group. Baseline weight was between 98.5 kg (placebo group) and 102.0 kg (for the rimonabant 20-mg/day dose). During the run-in, there was a mean −1.9-kg weight loss. From baseline at the end of the run-in those in placebo the group who completed the trial lost an additional −2.3 kg, the low-dose rimonabant group (5 mg/day) lost −3.6 kg, and the high-dose group (20 mg/day) lost −8.6 kg. On an intent-to-treat basis these numbers were a weight loss of −1.8 kg for the placebo group, −3.4 kg for the 5-mg/day group, and −6.6 kg for the 20-mg/day group. Expressing the data as a responder analysis, the authors reported that 30.5% of the placebo group lost ≥5%, compared with 44.2% for the 5-mg/day and 67.4% for the 20-mg/day dose of rimonabant. When a weight loss of ≥10% was considered, the numbers were 12.4% for the placebo group, 15.3% for the 5 mg/day dose of rimonabant group, and 39% for the 20-mg/day dose group. Waist circumference was also reduced by treatment. With the intent-to-treat analysis, waist declined 2.4 cm in the placebo group, 3.9 cm in the 5-mg/day dose group, and 6.5 cm

in the 20-mg/day dose group. Triglycerides were reduced by 6.8% in the 20-mg/day group compared with a rise of 8.3% in the placebo group. HDL cholesterol increased by 22.3% compared with 13.4% in the placebo group. These changes in metabolic parameters were reflected in a change in the prevalence of the metabolic syndrome. Among those in the placebo group who completed the study, there was a 33.9% reduction in the prevalence of the metabolic syndrome, compared with 34.8% in the 5-mg/day rimonabant dose group and 64.8% in the 20-mg/day dose group. In the 20-mg/day group the LDL particle size increased, adiponectin increased, glucose decreased, insulin decreased, C-reactive protein decreased, and the metabolic syndrome prevalence was cut in half. There was no significant change in blood pressure or pulse among the groups.

Discontinuation for adverse events was similar, but the reasons were different. Among placebo-treated patients, it was for lack of weight loss. With the higher dose of rimonabant (20 mg/day) depressed mood disorders, nausea, vomiting, diarrhea, headache, dizziness, and anxiety were all more common than in the placebo group. The Hospital Anxiety and Depression scale scores were not significantly different among treatment groups.

Slightly more patients withdrew for drug-related adverse events in the 5-mg/day dose group and even more with the 20-mg/day dose relative to those receiving placebo. The major reasons for withdrawal were psychiatric, nervous system, and gastrointestinal track symptoms. The complaints, which occurred with >5% frequency in the drug-treated patients, included upper respiratory tract infection, nasopharyngitis, nausea, influenza, diarrhea, arthralgia, anxiety, insomnia, viral gastroenteritis, dizziness, depressed mood, and fatigue in the 20-mg/day dose group (Pi-Sunyer et al., 2006).

The second study was in dyslipidemic patients and was called the Rimonabant in Obesity-Lipids (RIO-Lipids) study (Despres et al., 2005). This was a 12-month randomized, double-blind, placebo-controlled trial of rimonabant at 5- and 20-mg/day doses versus placebo in overweight subjects eating a 600-kcal/day deficit diet. It was conducted at 67 sites in eight countries. As a lipids trial, the inclusion criteria were a BMI of 27 to 40 kg/m^2, elevated fasting triglycerides (150–700 mg/dl), ratio of cholesterol to HDL-cholesterol >5 in men and >4.5 in women, and no more than 5-kg variation in body weight in the previous 3 months. Subjects were stratified at the run-in by triglycerides < or >400 mg/dl and at the end of run-in by a weight loss of > or <2 kg. Randomization was on a 1:1:1 basis of placebo, 5 mg/day of rimonabant, and 20 mg/day of rimonabant. After the end of the 4-week run-in participants, were randomized and treated for 12 months; the dropout rate was ~40% by the end of 12 months. Weight losses in this trial were almost identical to those in the Rio-Europe trial. After an ~2-kg weight loss during the run-in, the patients in the placebo group who completed the trial lost an additional −2.3 kg, compared with −4.2 kg in the 5-mg/day rimonabant dose group and −8.8 kg in the 20-mg/day dose group. Waist circumference also showed a dose-dependent reduction of −3.4 cm in the placebo group, −4.9 cm in the 5-mg/day dose group, and −9.1 cm in the 20-mg/day dose group.

A number of other metabolic parameters also responded to the drug or weight loss. These included a decrease in triglycerides, an increase in HDL cholesterol, a decrease in peak size of LDL cholesterol particles, an increase in adiponectin, a decline in fasting insulin, a fall in leptin and a decrease in C-reactive protein. Several liver enzymes fell with treatment, suggesting improvement in nonalcoholic steatosis. Blood pressure decreased significantly in RIO-Lipids in contrast with RIO-Europe. As might be expected from these metabolic changes, the prevalence of the metabolic syndrome in those who met the Adult Treatment Panel III criteria at randomization fell to 25.8% in the 20-mg/day group, to 40.0% in the 5-mg/day group, and to 41.0% in the placebo group.

The third randomized, double-blind, placebo-controlled study, called RIO-North America, was also a 2-year study in which randomized 3045 overweight subjects with a BMI >30 kg/m^2 or with a BMI >27 kg/m^2 with treated or untreated hypertension or dyslipidemia and without diabetes to placebo, 5 mg/day of rimonabant, or 20 mg/day of rimonabant. Participants were instructed on a 600-kcal/day deficit diet. Randomization and baseline occurred after a 4 week run-in period in which subjects lost an average of −1.9 kg. They were thus stratified by whether they lost > or <2 kg during the run-in. At 1 year, half of the patients in each drug group were switched to placebo on the basis of their initial randomization. The trial was conducted at 64 American and 8 Canadian centers. At 1 year, completion rates were 51 to 55% for the three arms. During the 1st year, weight loss was −2.8 kg in the placebo group and −8.6 kg in the 20-mg/day rimonabant group (Fig. 9). Weight loss declined steadily until week 36, after which it plateaued. For the 2nd year, those individuals who were switched from rimonabant to placebo regained weight at almost the mirror image of the rate at which they lost it during the 1st year. At the end of the study they were still slightly lighter, but no different from the group treated with placebo for the full 2 years. Waist circumference decreased, and the percentage with the metabolic syndrome decreased from 34.8 to 21.2% in the 20-mg/day group compared with a change from 31.7 to 29.2% in the placebo group. HDL cholesterol rose more in the rimonabant group treated with 20 mg/day than placebo, and triglycerides fell more in the participants receiving the higher dose of rimonabant. Patients with depression were not included in this study. Adverse events leading to discontinuation of the study were

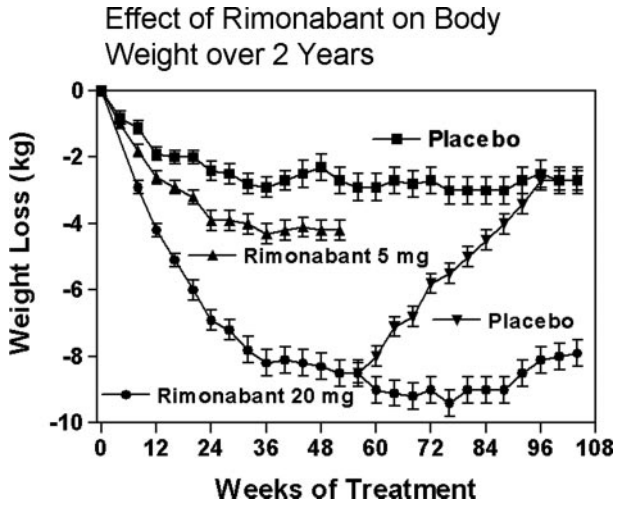

FIG. 9. Effect on body weight of rimonabant in a 2-year, randomized, placebo-controlled clinical trial. Adapted from *The Journal of the American Medical Association*, volume 295, pp 761–775. Copyright © 2006 American Medical Association.

higher in the rimonabant-treated than in the placebo-treated participants. However, the profile and effectiveness of this agent seem very promising for treatment of obesity and the physical and laboratory findings that make up the metabolic syndrome.

c. Studies in special populations.

i. Diabetic patients. The fourth study, RIO-Diabetes, was conducted in type 2 diabetic patients. In it, 1045 diabetic subjects treated with diet, metformin, or sulfonylurea drugs at 151 centers in 11 countries were randomized to treatment over 1 year with placebo or rimonabant at 5 or 20 mg/day. Weight loss in the placebo group was −1.4 kg, compared with −2.3 kg in the 5-mg/day group and −5.3 kg in the 20-mg/day group. Triglycerides and blood pressure declined more in the subjects treated with 20-mg/day rimonabant. Of those who completed the trial, 55.9% lost >5% of body weight during treatment with 20-mg/day rimonabant compared with 19.5% in the placebo-treated group (Scheen et al., 2006).

ii. Prevention of weight gain after cessation of smoking. Studies with rimonabant suggest that it can slow or prevent the weight gain of individuals who have quit smoking.

d. Safety considerations. Because this drug "dampens" the feedback systems for pleasurable responses, there is concern about its behavioral effects. To quote from the most recently published article (Scheen et al., 2006), "A slightly greater proportion of patients in the rimonabant treatment groups experienced adverse events than did those in the placebo group." The events occurring at a frequency of >5% in the rimonabant group included nausea, diarrhea, vomiting, dizziness, hypoglycemia, fatigue, and anxiety, all of which were generally mild or moderate. Discontinuation for adverse events was also more common in the higher-dose rimonabant group. The most common events for discontinuation were depressed mood disorders, nausea, and dizziness.

e. Other cannabinoid antagonists. Other cannabinoid antagonists are said to be under clinical development and may have entered phase III trials.

B. Drugs Approved by the U.S. Food and Drug Administration for Short-Term Treatment of Overweight Patients

1. Sympathomimetic Drugs.

a. Mechanism of action. Phentermine, diethylpropion, benzphetamine, and phendimetrazine behave in many ways like the adrenergic neurotransmitters and are thus called "sympathomimetic amines" (Bray and Greenway, 1999). They were originally thought to "release" norepinephrine from vesicular stores, but more recent data suggest that they act primarily to inhibit reuptake of norepinephrine and dopamine at nerve endings.

b. Clinical studies. Most of the data on phentermine, diethylpropion, benzphetamine, and phendimetrazine come from short-term trials (Bray and Greenway, 1999). One of the longest of these clinical trials lasted 36 weeks and compared placebo treatment with continuous phentermine or intermittent phentermine (Munro et al., 1968). Both continuous and intermittent phentermine therapy produced more weight loss than placebo. In the drug-free periods, the patients treated intermittently slowed their weight loss, only to lose weight more rapidly when the drug was reinstituted.

In their analysis of pharmacotherapy for treatment of the overweight patient, Haddock et al. (2002) compiled data on both phentermine and diethylpropion. They found that in six studies, phentermine produced a mean weight loss of −6.3 kg (range −3.6 to −8.8 kg) compared with a placebo-induced weight loss of −2.8 kg (range −1.5 to − 5.2 kg). For diethylpropion, the mean weight loss in nine studies was −6.5 kg (range −1.9 to − 13.1 kg), and for the placebo group it was −3.5 kg (range −0.4 to − 10.5 kg). Similar data for benzphetamine are −4.03 kg (range −1.6 to − 7.3 kg) and for placebo −0.73 kg (range −1.3 to − 2.0 kg).

Phentermine and diethylpropion are classified by the U.S. Drug Enforcement Agency as schedule IV drugs; benzphetamine and phendimetrazine are schedule III drugs. This regulatory classification indicates the U.S. Government's belief that they have the potential for abuse, although this potential seems to be very low. Phentermine and diethylpropion are approved for only a "few weeks," which usually is interpreted as up to 12 weeks. Weight loss with phentermine and diethylpropion persists for the duration of treatment, suggesting that tolerance does not develop to these drugs. If tolerance were to develop, the drugs would be expected to lose their effectiveness, and patients would require increased amounts of the drug to maintain weight loss. This does not occur.

IV. Antidepressant and Antiepileptic Drugs That Produce Weight Loss but Are Not Approved by the U.S. Food and Drug Administration for Weight Loss

A. Fluoxetine and Sertraline

1. Mechanism of Action. Fluoxetine and sertraline are both selective serotonin reuptake inhibitors that block the transporters that remove serotonin from the neuronal cleft into the presynaptic space for metabolism by monoamine oxidase or storage in granules. They also reduce food intake. In a 2-week placebo-controlled trial, fluoxetine at a dose of 60 mg/day produced a 27% decrease in food intake (Lawton et al., 1995).

2. Clinical Studies. Both fluoxetine and sertraline are approved by the FDA for treatment of depression. In clinical trials with depressed patients lasting 8 to 16 weeks, sertraline gave an average weight loss of −0.45 to −0.91 kg. Fluoxetine at a dose of 60 mg/day (three times the usual dose for treatment of depression) was evaluated in clinical trials for the treatment of overweight patients by Eli Lilly & Co. A meta-analysis of six studies showed a wide range of results with a mean weight loss in one study of −14.5 kg and a weight gain of +0.40 kg in another (Li et al., 2005). In the meta-analysis by Avenell et al. (2004), the weight loss at 12 months was −0.33 kg (95% CI −1.49 to 0.82 kg). Goldstein et al. (1995) reviewed the trials with fluoxetine that included one 36-week trial in type 2 diabetic subjects, a 52-week trial in subjects with uncomplicated overweight, and two 60-week trials in subjects with dyslipidemia, diabetes, or both. A total of 1441 subjects were randomized to fluoxetine (719) or placebo (722); 522 subjects receiving fluoxetine and 504 subjects receiving placebo completed 6 months of treatment. Weight loss in the placebo and fluoxetine groups at 6 months and 1 year were −2.2 and −4.8 kg and −1.8 and −2.4 kg, respectively. The recovery of 50% of the lost weight during the second 6 months of treatment with fluoxetine makes it inappropriate for the long-term treatment of overweight, which requires chronic treatment. Fluoxetine and sertraline, although not good antioverweight drugs, may be preferred in the depressed obese patient over some of the tricyclic antidepressants that are associated with significant weight gain (Fig. 10).

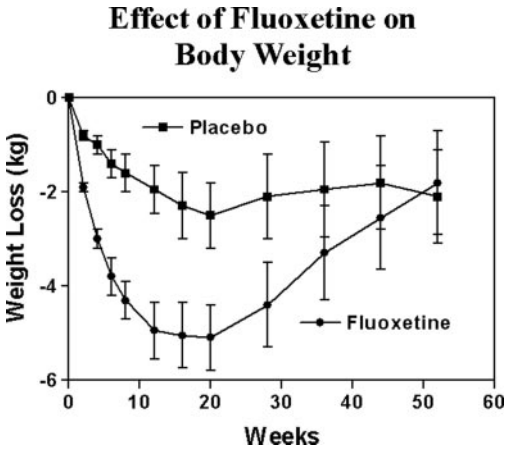

FIG. 10. Effect on body weight of fluoxetine from pooled data of randomized, placebo-controlled clinical trials. Redrawn from Goldstein et al. (1995).

B. Bupropion

1. Mechanism of Action. Bupropion is a norepinephrine and dopamine reuptake inhibitor that is approved for the treatment of depression and for smoking cessation.

2. Clinical Studies for Weight Loss. One clinical use for bupropion has been to prevent weight gain after cessation of smoking. It was thus a potential drug for treatment of overweight patients. In one clinical trial, 50 overweight subjects were randomized to bupropion or placebo for 8 weeks with a blinded extension for responders to 24 weeks. The dose of bupropion was increased to a maximum of 200 mg twice daily in conjunction with a calorie-restricted diet. At 8 weeks, 18 subjects in the bupropion group lost −6.2 ± 3.1% of body weight compared with −1.6 ± 2.9% for the 13 subjects in the placebo group ($P < 0.0001$). After 24 weeks, the 14 responders to bupropion lost −12.9 ± 5.6% of initial body weight, of which 75% was fat as determined by dual energy X-ray absorptiometry (Gadde et al., 2001).

Two multicenter clinical trials, one in obese subjects with depressive symptoms and one in uncomplicated overweight patients, followed this study. In the study of overweight patients with depressive symptom ratings of 10 to 30 on a Beck Depression Inventory, 213 patients were randomized to 400 mg of bupropion per day and 209 subjects to placebo for 24 weeks. The 121 subjects in the bupropion group who completed the trial lost −6.0 ± 0.5% of initial body weight compared with −2.8 ± 0.5% in the 108 subjects in the placebo group ($P < 0.0001$) (Jain et al., 2002). The study in uncomplicated overweight subjects randomized 327 subjects to 300 mg/day of bupropion, 400 mg/day of bupropion, or placebo in equal proportions. At 24 weeks, 69% of those randomized remained in the study and the percent losses of initial body weight were −5 ± 1, −7.2 ± 1, and −10.1 ± 1% for the placebo, 300 mg/day of bupropion, and 400 mg/day of bupropion groups, respectively ($P < 0.0001$). The placebo group was randomized to the 300- or 400-mg/day group at 24 weeks, and the trial was extended to week 48. By the end of the trial, the dropout rate was 41%, and the weight loss in the 300-mg/day bupropion and 400-mg/day bupropion groups was −6.2 ± 1.25% and −7.2 ± 1.5% of initial body weight, respectively (Anderson et al., 2002). Thus, it seems that nondepressed subjects may respond to bupropion with weight loss to a greater extent than those with depressive symptoms (Fig. 11). Because bupropion is at the end of its

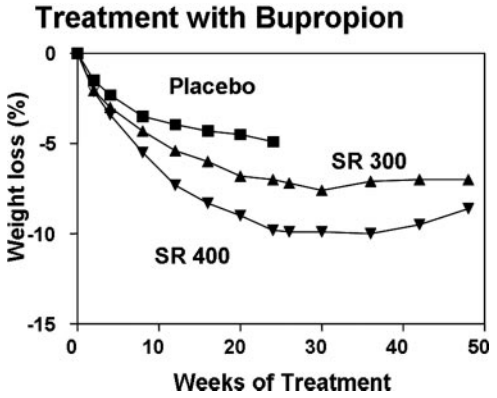

FIG. 11. Effect on body weight of bupropion in a randomized, placebo-controlled clinical trial. Adapted from Anderson et al. (2002).

patent life, it is not being developed for obesity, but similar drugs in this class would be obvious candidates.

C. Topiramate

1. Mechanism of Action. Topiramate is a neurotherapeutic agent that is approved for treatment of selected seizure disorders. It is a weak carbonic anhydrase inhibitor, exhibiting selectivity for carbonic anhydrase isoforms II and IV. Topiramate also modulates the effects at receptors for the GABA-A receptor and the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate subtype of the glutamate receptor. This drug also exhibits state-dependent blockade of voltage-dependent Na^+ or Ca^{2+} channels. These mechanisms are believed to contribute to its antiepileptic properties. The modulation of GABA receptors may provide one potential mechanism to reduce food intake, although other mechanisms, yet to be described, may be more important in defining its effects on body weight (Astrup and Toubro, 2004). The final words on the mechanism(s) by which topiramate reduces food intake and body weight are yet to be published.

2. Clinical Studies for Weight Loss. Topiramate is an antiepileptic drug that was discovered to give weight loss in the clinical trials for epilepsy. Weight losses of −3.9% of initial weight were seen at 3 months and losses of −7.3% of initial weight were seen at 1 year (Ben-Menachem et al., 2003). Bray et al. (2003) reported a 6-month, placebo-controlled, dose-ranging study of 385 obese subjects who were randomized to placebo or topiramate at 64, 96, 192, or 384 mg/day. These doses were gradually reached by a tapering increase and were reduced in a similar manner at the end of the trial. Weight loss from baseline to 24 weeks was −2.6, −5, −4.8, −6.3, and −6.3% in the placebo, 64-, 96-, 192-, and 384-mg/day groups, respectively. The most frequent adverse events were paresthesias, somnolence and difficulty with concentration, memory, and attention.

This trial was followed by two multicenter trials. The first trial randomized 1289 obese subjects to topiramate 89, 192, or 256 mg/day. This trial was terminated early because of the sponsor's decision to pursue a time-release form of the drug. The 854 subjects who completed 1 year of the trial before it was terminated lost −1.7, −7, −9.1, and −9.7% of their initial body weight in the placebo, 89-, 192-, and 256-mg/day groups, respectively. Subjects in the topiramate groups had significant improvement in blood pressure and glucose tolerance (Wilding et al., 2004). The second trial enrolled 701 subjects who were treated with a very low-calorie diet to induce an 8% loss of initial body weight. The 560 subjects who achieved an 8% weight loss were randomized to 96 or 192 mg/day of topiramate or placebo. The sponsor also terminated this study early. At the time of termination, 293 subjects had completed 44 weeks. The topiramate groups lost 15.4 and 16.5% of their baseline weight whereas the placebo group lost 8.9% (Astrup et al., 2004). Although topiramate is still available as an antiepileptic drug, the development program to obtain an indication for overweight was terminated by the sponsor because of the associated adverse events (Fig. 12).

3. Special Situations. Topiramate has also been evaluated in the treatment of binge-eating disorder. Thirteen women with binge-eating disorder were treated in an open-label study using a mean dose of 492 mg/day of topiramate. The binge-eating disorder symptoms improved, and weight loss was observed (Shapira et al., 2000). This open-label study was followed by a randomized, controlled trial of 14 weeks in subjects with binge-eating disorder. Sixty-one subjects were randomized to 25 to 600 mg/day of topiramate or placebo in a 1:1 ratio. The topiramate group had improvement in binge eating symptoms and lost −5.9 kg at an average topiramate dose of 212 mg/day (McElroy et al., 2003). The 35 subjects who completed this trial were given the opportunity to participate in an open-label extension. The topiramate-treated subjects continued to maintain improvement in binge-eating symptoms and weight (McElroy et al., 2004b).

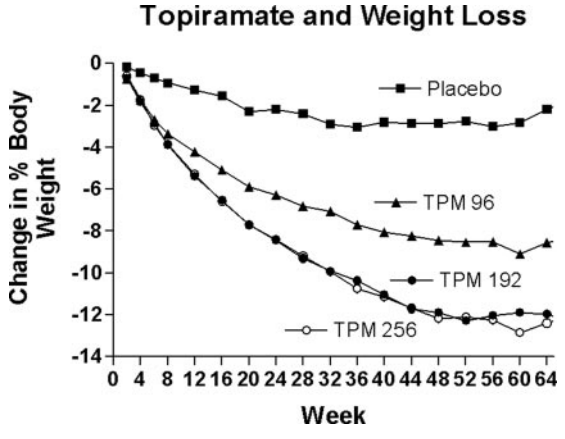

FIG. 12. Effect on body weight of topiramate in a double-blind, randomized, placebo-controlled dose-ranging clinical trial. Adapted from Bray et al. (2003).

Topiramate has also been used to treat patients with the Prader-Willi syndrome. Three subjects with Prader-Willi syndrome were treated with topiramate and had a reduction in the self-injurious behavior that is associated with this uncommon genetic disease (Shapira et al., 2002). A second study in seven additional subjects confirmed these findings (Smathers et al., 2003). A third study evaluated appetite, food intake, and weight. Although the self-injurious behavior improved, there was no effect on these other parameters (Shapira et al., 2004). Topiramate was also used to treat two subjects with nocturnal eating syndrome and two subjects with sleep-related eating disorder. There was an improvement in all subjects and a −11-kg weight loss over 8.5 months with an average topiramate dose of 218 mg/day (Winkelman, 2003).

D. Zonisamide

1. Mechanism of Action. Zonisamide is an antiepileptic drug that has serotonergic and dopaminergic activity in addition to inhibiting sodium and calcium channels. The mechanism by which it lowers body weight has not been clarified.

2. Clinical Studies for Weight Loss. Weight loss was noted in the clinical trials for the treatment of epilepsy, again suggesting a potential agent for weight loss. Gadde et al. (2003) tested this possibility by performing a 16-week randomized, controlled trial in 60 obese subjects. Subjects were placed on a calorie-restricted diet and randomized to zonisamide or placebo (Fig. 13). The zonisamide was started at 100 mg/day and increased to 400 mg/day. At 12 weeks, the dose of zonisamide for those subjects who had not lost 5% of initial body weight was increased to 600 mg/day. The zonisamide group lost −6.6% of initial body weight at 16 weeks compared with −1% in the placebo group. Thirty-seven subjects completing the 16-week trial elected to continue to week 32. Of these, 20 were in the zonisamide group and 17 were in the placebo group. At the end of 32 weeks, the 19 subjects who remained in the zonisamide group lost −9.6% of their initial body weight compared with −1.6% for the 17 subjects in the placebo group.

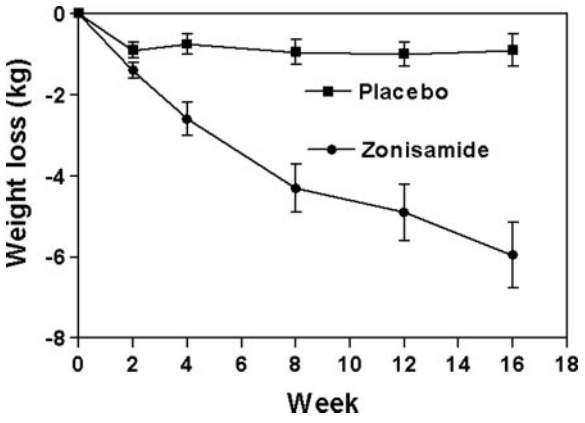

FIG. 13. Effect on body weight of zonisamide in a randomized, placebo-controlled clinical trial. Redrawn from *The Journal of the American Medical Association*, volume 289, pp 1820–1825. Copyright © 2003 American Medical Association.

McElroy et al. (2004a) evaluated zonisamide in an open-label prospective trial in subjects with binge-eating disorder. Fifteen subjects were treated with doses of 100 to 600 mg/day for 12 weeks. The eight subjects who completed the trial had an average dose of 513 mg/day, experienced an improvement in their binge-eating symptoms and lost a significant amount of weight.

E. Lamotrigine

1. Mechanism of Action. Lamotrigine is an antiepileptic drug that does not produce weight gain (Devinsky et al., 2000).

2. Clinical Studies. A recent double-blind, randomized, placebo-controlled trial examined the effects of placebo versus lamotrigine escalated from 25 to 200 mg/day on weight loss in a 26-week trial with 40 healthy overweight (BMI 30–40 kg/m^2) adults >18 years of age. At the end of the trial body weight was marginally lower (P = 0.062) in the lamotrigine-treated group (−6.4 kg) than in the placebo-treated group (−1.2 kg) (Merideth, 2006).

V. Drugs Approved by the U.S. Food and Drug Administration for Uses Other Than Overweight

A. Metformin

1. Mechanism of Action. Metformin is a biguanide that is approved for the treatment of diabetes mellitus, a disease that is exacerbated by overweight and weight gain. This drug reduces hepatic glucose production, decreases intestinal absorption from the gastrointestinal tract, and enhances insulin sensitivity.

2. Clinical Studies. In clinical trials in which metformin was compared with sulfonylureas, it produced weight loss (Bray and Greenway, 1999). In one French trial, Biguanides and Prevention of Risks in Obesity (BIGPRO), metformin was compared with placebo in a 1-year multicenter study in 324 middle-aged subjects with upper body adiposity and the insulin resistance syndrome (metabolic syndrome). The subjects receiving metformin lost significantly more weight (1–2 kg) than the placebo group, and the conclusion of the study was that metformin may have a role in the primary prevention of type 2 diabetes (Fontbonne et al., 1996). In a meta-analysis of three of these studies Avenell et al. (2004) reported a weighted mean weight loss at 12 months of −1.09 kg (95% CI −2.29 to 0.11 kg).

The best trial of metformin is the Diabetes Prevention Program study of individuals with impaired glucose tolerance. The main part of this study included three treatment arms to which participants were randomly assigned, if they were >25 years of age, had a BMI >24 kg/m^2 (except Asian-Americans who only needed a BMI ≥22 kg/m^2), and had impaired glucose tolerance. The three primary arms included lifestyle (n = 1079 partic-

ipants), metformin ($n = 1073$), and placebo ($n = 1082$). During the follow-up averaging 3.2 years, the metformin-treated group lost 2.5% of their body weight ($P < 0.001$, compared with placebo), and the conversion from impaired glucose tolerance to diabetes was reduced by 30% compared with placebo (Fig. 14). In the DPP trial, metformin was more effective in reducing the development of diabetes in the subgroup who were most overweight and in the younger members of the cohort (Knowler et al., 2002).

Although metformin does not produce enough weight loss (5%) to qualify as a "weight-loss drug" according to the FDA criteria, it would seem to be a very useful choice for overweight individuals who have diabetes or are at high risk for diabetes. One area for use of metformin is treatment of women with the polycystic ovary syndrome in whom a modest weight loss may contribute to increased fertility and reduced insulin resistance (Ortega-Gonzalez et al., 2005).

Metformin (850 mg) b.i.d. and 120 mg of orlistat t.i.d. were compared with 10 mg of sibutramine daily in obese subjects over 6 months. BMI decreased by −9.1, −9.9, and −13.6%, respectively. Weight loss was greater in the sibutramine group than in either the metformin or orlistat groups ($P < 0.001$) (Gokcel et al., 2002).

B. Pramlintide

1. Mechanism of Action. Amylin is peptide found in the β-cell of the pancreas. It is secreted along with insulin, and circulates in the blood. Amylin is deficient in type I diabetes in which β-cells are immunologically destroyed. Pramlintide is a synthetic amylin analog with a prolonged biological half-life (Riddle and Drucker, 2006).

2. Clinical Studies. Pramlintide is approved by the FDA for the treatment of diabetes. Unlike insulin, sulfonylureas, and thiazolidinediones, pramlintide is associated with weight loss. In a study of 651 subjects with type 1 diabetes randomized to placebo or subcutaneous pramlintide 60 μg three or four times a day along with an insulin injection, the hemoglobin A_{1c} decreased −0.29 to 0.34% and weight decreased −1.2 kg in the pramlintide group relative to placebo (Ratner et al., 2004). Maggs et al. (2003) analyzed the data from two 1-year studies in insulin-treated type II diabetic subjects randomized to pramlintide 120 μg twice a day or 150 μg three times a day. Weight decreased by −2.6 kg and hemoglobin A_{1c} decreased −0.5%. When weight loss was then analyzed by ethnic group, African Americans lost −4 kg, Caucasians lost −2.4 kg, and Hispanics lost −2.3 kg, and the improvement in diabetes correlated with the weight loss, suggesting that pramlintide is effective in ethnic groups with the greatest burden from overweight. The most common adverse event was nausea, which was usually mild and confined to the first 4 weeks of therapy.

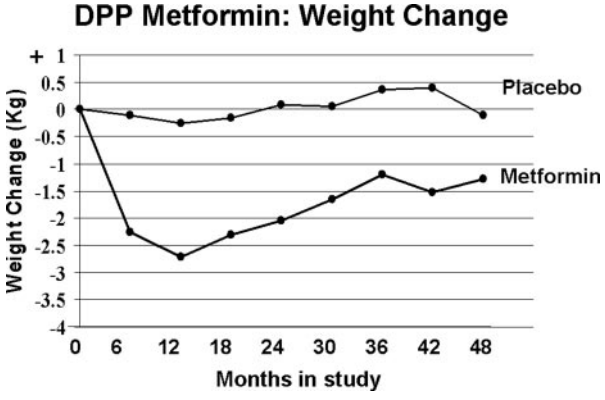

FIG. 14. Effect on body weight of metformin in a double-blind, placebo-controlled, randomized trial from the Diabetes Prevention Program. Data from Knowler et al. (2002).

C. Exenatide

1. Mechanism of Action. GLP-1 is derived from the processing of the preproglucagon peptide, which is secreted by L-cells in the terminal ileum in response to a meal. Increased GLP-1 inhibits glucagon secretion, stimulates insulin secretion, stimulates gluconeogenesis, and delays gastric emptying (Patriti et al., 2004). It has been postulated to be responsible for the superior weight loss and superior improvement in diabetes seen after gastric bypass surgery for overweight (Greenway et al., 2002; Small and Bloom, 2004). GLP-1 is rapidly degraded by dipeptidyl peptidase-4, an enzyme that is elevated in the obese. Bypass operations for overweight increase levels of GLP-1, but do not change the levels of dipeptidyl pepidase-4 (Lugari et al., 2004; Riddle and Drucker, 2006).

Exenatide (exendin-4) is a 39-amino acid peptide that is produced in the salivary gland of the Gila monster lizard. It has 53% homology with GLP-1, but it has a much longer half-life. Exenatide decreases food intake and body weight gain in Zucker rats while lowering hemoglobin A_{1c} (Szayna et al., 2000). It also increases β-cell mass to a greater extent than would be expected for the degree of insulin resistance (Gedulin et al., 2005). Exendin-4 induces satiety and weight loss in Zucker rats with peripheral administration and crosses the blood-brain barrier to act in the central nervous system (Rodriquez de Fonseca et al., 2000; Kastin and Akerstrom, 2003).

2. Clinical Studies with Weight Loss as a Component. Exenatide has been approved by the U.S. Food and Drug Administration for treatment of type 2 diabetic patients whose diabetes is inadequately controlled with either metformin or sulfonylureas. In humans, exenatide reduces fasting and postprandial glucose levels, slows gastric emptying, and decreases food intake by 19% (Edwards et al., 2001). The side effects of exenatide in humans are headache, nausea, and vomiting that are lessened by gradual dose escalation (Fineman et al., 2004). Several clinical trials of 30 weeks' duration using exenatide at 10 μg s.c./day or a placebo have been reported (Buse et al., 2004; DeFronzo et al., 2005; Kendall

et al., 2005). In one trial with 377 type 2 diabetic subjects in whom maximal sulfonylurea therapy was failing, exenatide produced a 0.74% greater fall in hemoglobin A_{1c} than placebo. Fasting glucose also decreased, and there was a progressive weight loss of 1.6 kg (Buse et al., 2004). The interesting feature of this weight loss is that it occurred without lifestyle changes, diet, or exercise (Fig. 15). Two of the 30-week exenatide trials contained an open-label extension to 82 weeks. Those completing the 82 weeks of exenatide treatment at 10 μg twice a day lost 5.3 kg in the trial with 150 subjects and 4.4 kg in the trial with 334 subjects (Blonde et al., 2006; Ratner et al., 2006). In a 26-week randomized, controlled trial, exenatide produced a 2.3-kg weight loss compared with a gain of 1.8 kg in the group receiving insulin glargine (Heine et al., 2005). A long-acting release form of exenatide is being developed. A press release by Eli Lilly & Co. described a 3.8-kg weight loss in diabetic subjects treated with this formulation given weekly for 15 weeks.

D. Somatostatin

1. Mechanism of Action. Somatostatin is a small peptide that is released in the GI tract and in the brain. It inhibits the release of most peptides, including insulin, glucagon, and growth hormone, among others.

2. Clinical Studies for Weight Loss. Overweight due to hypothalamic injury has been associated with insulin hypersecretion (Bray and Gallagher, 1975). Lustig et al. (1999) treated eight children with overweight due to hypothalamic damage with octreotide injections to decrease insulin hypersecretion. These children gained 6 kg in the 6 months before octreotide treatment and lost −4.8 kg in the 6 months of treatment with octreotide, an analog of somatostatin. The weight loss was correlated with a reduction in insulin secretion on a glucose tolerance test. This open-label trial was followed by a randomized, controlled trial of octreotide treatment in children with hypothalamic overweight. The subjects received octreotide 5 to 15 μg/kg/day or placebo for 6 months. The children receiving octreotide gained 1.6 kg compared with 9.1 kg for those in the placebo group (Lustig et al., 2003). This same group of investigators postulated that there might be a subset of obese subjects who were insulin hypersecretors and that these subjects would respond to treatment with octreotide by losing weight. After an oral glucose tolerance test in which glucose and insulin were measured, 44 subjects were treated with long-acting 40-mg/month octreotide for 6 months. These subjects lost weight, reduced food intake, and reduced carbohydrate intake. Weight loss was greatest in those with insulin hypersecretion, and the amount of weight loss was correlated with the reduction in insulin hypersecretion (Velasquez-Mieyer et al., 2003). In a multicenter randomized, controlled trial, 172 obese subjects (144 women and 28 men) who had insulin hypersecretion during a glucose tolerance test at screening received long-acting octreotide in doses of 20, 40, or 60 mg/month or placebo for 6 months. The greatest weight loss was 3.5 to 3.8% of initial body weight in the two higher dose groups, an amount that was statistically significant, but not enough to meet the criteria for approval by the FDA (Lustig et al., 2006).

Octreotide has been shown to decrease gastric emptying (Foxx-Orenstein et al., 2003). Treatment of patients with the Prader-Willi syndrome who have elevated ghrelin levels does not cause weight loss, but ghrelin levels are normalized. The reason for the lack of weight loss was postulated to be the reduction of PYY, a satiating gastrointestinal hormone that was also decreased (Tan et al., 2004).

E. Atomoxetine

1. Mechanism of Action. Atomoxetine is a central norepinephrine uptake inhibitor approved for the treatment of attention-deficit/hyperactivity disorder.

2. Clinical Study for Weight Loss. Thirty obese women were randomized to atomoxetine increasing from 25 to 100 mg/day or placebo in a 12-week trial. The atomoxetine group lost 3.8 kg more weight than the placebo group, and the drug seemed to be well tolerated (Gadde et al., 2006).

F. Growth Hormone and Growth Hormone Fragment

1. Mechanism of Action. Growth hormone is a pituitary peptide that is essential for the adolescent growth spurt. Bioengineered growth hormone is widely used to treat short stature as well as growth hormone deficiency in adults (Hoffman et al., 2004) and has been used by athletes to build muscle, as one of its effects is to enhance protein accretion. Growth hormone has been consistently shown to increase body protein and to reduce total body fat and particularly visceral fat, making it a potential agent to treat the overweight patient.

2. Clinical Studies on Body Composition. In a small clinical trial, 18 overweight patients with newly diag-

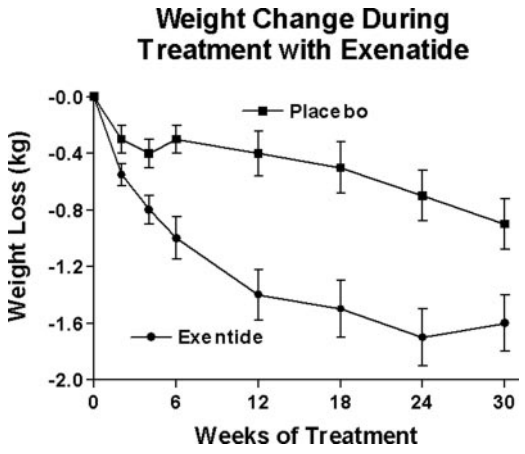

FIG. 15. Effect on body weight of exenatide in a randomized, placebo-controlled clinical trial. Copyright © 2005 American Diabetes Association. From Diabetes Care®, Vol. 28, 2005; 1083–1091. Adapted with permission from *The American Diabetes Association*.

nosed diabetes were randomly assigned to placebo or growth hormone injection along with dietary restriction in a double-blind study (Nam et al., 2001). These authors found a greater decrease in visceral fat, an increase in lean body mass, and improved insulin sensitivity during this 12-week trial. In a 12-month randomized double-blind, placebo-controlled clinical trial, 40 postmenopausal women were assigned to daily placebo injections or injections of growth hormone (0.67 mg/day). After 1 year Franco et al. (2005) reported that the women had significantly reduced abdominal and visceral adiposity, improved insulin sensitivity, and improved total and low-density lipoprotein cholesterol concentrations.

A group working in Australia has identified a fragment of growth hormone that is lipolytic. This compound, called AOD9604, is a modified fragment of the amino acids from 177 to 191 in growth hormone. It is orally active and is said to bind to the fat cell, stimulating lipolysis and inhibiting reesterification without stimulating growth. A 12-week multicenter trial randomized 300 obese subjects to one of five daily doses (1, 5, 10, 20, and 30 mg) of AOD9604 or placebo. The 1-mg dose was the most effective for weight loss. Subjects receiving the 1-mg dose lost −2.6 kg compared with −0.8 kg in the placebo group, and the rate of weight loss was constant throughout the trial (http://www.metabolic.com.au/files/T5SH4035T6/ASX_%20AOD9604_result-%20announcement.pdf). Phase III trials are evidently in the planning stages.

VI. Drugs with Clinical Data or in Clinical Studies

A. Leptin

1. Mechanism of Action. Leptin is a cytokine that acts on the gp130 family of cytokine receptors in the hypothalamus to activate the Janus kinase signal transduction and translation system (JAK-STAT). The lack of leptin, a hormone derived primarily from the fat cell, causes massive overweight in animals and humans. Its replacement reverses the overweight associated with the deficiency state. The discovery of leptin generated hope that leptin would be an effective treatment for overweight.

2. Clinical Studies. Leptin at subcutaneous doses of 0 (vehicle), 0.01, 0.05, 0.1, and 0.3 mg/kg daily was tested in lean and obese humans of both sexes. Lean subjects were treated for 4 weeks and lost −0.4 to −1.9 kg. Obese subjects were treated for 24 weeks and a dose-response relationship for weight loss was seen with the 0.3-mg/kg group losing −7.1 kg (Heymsfield et al., 1999). Pegylated leptin allows for weekly, rather than daily, injections. Although pegylated leptin at 20 and 60 mg/week in obese subjects over 8 to 12 weeks did not produce more weight loss than placebo, the pegylated leptin at 80 mg weekly combined with a very low-calorie diet for 46 days produced 2.8 kg more weight loss in 12 subjects randomized to leptin compared with the 10 subjects randomized to placebo ($P < 0.03$) (Hukshorn et al., 2003).

Leptin has been found to ameliorate many of the symptoms of lipodystrophy. Nine female patients with lipodystrophy and serum leptin levels of <4 ng/ml were treated with recombinant methionyl human leptin for 4 months. Eight of the women had diabetes. During treatment with leptin, glycosylated hemoglobin decreased an average of 1.9% During the 4 months of therapy, triglyceride levels decreased by 60%. Liver volume was also reduced by an average of 28% and resting metabolic rate decreased significantly with therapy (Oral et al., 2002). A reduction in body weight produced by eating a low-calorie diet is associated with decreased 24-h energy expenditure and decreased leptin and thyroid hormone levels. When body weight was reduced by 10%, circulating triiodothyronine, thyroxine, and leptin concentrations were decreased. All of these endocrine changes were reversed by administration of "replacement" doses of recombinant human methionyl-leptin. Total energy expenditure increased in all subjects during treatment with leptin, indicating that decreased leptin may account for some aspects of the endocrine adaptations to weight loss (Rosenbaum et al., 2002).

Leptin has been evaluated in combination with amylin in rodents with diet-induced obesity (Roth et al., 2006). Leptin treatment gave a weight gain of 0.6% of body weight, amylin gave a weight loss of 3.4% of body weight, and the combination gave a weight loss of 7.1% body weight. In another pair-feeding experiment, the leptin- and amylin-treated rats lost 12% of body weight compared with only 6.9% in the pair-fed group, suggesting that both a reduction in food intake and an increase in metabolic rate are responsible for the weight loss. These findings suggest that amylin restores sensitivity to leptin.

B. Neuropeptide Y Receptor Antagonists

1. Mechanism of Action. Neuropeptide Y is a widely distributed neuropeptide that has five receptors: Y_1, Y_2, Y_4, Y_5, and Y_6. Neuropeptide Y stimulates food intake, inhibits energy expenditure, and increases body weight by activating Y_1 and Y_5 receptors in the hypothalamus (Parker et al., 2002). Levels of NPY in the hypothalamus are temporally related to food intake and are elevated with energy depletion. Surprisingly, NPY knockout mice have no phenotype. NPY_5 receptor antagonists fall into two categories, those that reduce food intake and those that do not, but those that do seem to do so through a mechanism separate from the Y_5 receptor. Thus, one group concluded that Y_5 receptor antagonists do not seem promising as antioverweight agents (Levens and Della-Zuana, 2003). In contrast, Y_1 receptor antagonists seem to have greater potential as antioverweight agents. A dihydropyridine neuropeptide Y_1 antagonist inhibited NPY-induced feeding in satiated rats (Poindexter et al.,

2002). Another Y_1 receptor antagonist J-104870, suppressed food intake when given orally to Zucker rats (Kanatani et al., 2001).

2. Clinical Studies. A study measuring NPY in obese humans casts doubt on the importance of the NPY antagonists in the treatment of overweight in humans. Obese women had lower NPY levels than lean women, and weight loss with a 400-kcal/day diet and adrenergic agonists (caffeine and ephedrine or caffeine, ephedrine, and yohimbine) did not change NPY levels at rest or after exercise (Zahorska-Markiewicz et al., 2001).

Several clinical trials with a selective Y_5 receptor antagonist have been completed. The first was a 2-year randomized, placebo-controlled trial (Erondu et al., 2006). It included two doses (Fig. 16). The second trial was designed to test the effect of the antagonist on the prevention of weight gain induced by providing patients with a very low-calorie diet before randomization.

C. Serotonin 2C Receptor Agonists

1. Mechanism of Action. Mice lacking the $5HT_{2C}$ receptor have increased food intake, because they take longer to be satiated. These mice also are resistant to fenfluramine, a serotonin agonist that causes weight loss. A human mutation of the $5HT_{2C}$ receptor has been identified that is associated with early-onset human obesity (Gibson et al., 2004; Nilsson, 2006). The precursor of serotonin, 5-hydroxytryptophan, reduces food intake and body weight in clinical studies (Cangiano et al., 1992, 1998). Fenfluramine (Rogers and Blundell, 1979; (Foltin et al., 1996) and dexfenfluramine (Drent et al., 1995), two drugs that act on the serotonin system, but were withdrawn from the market in 1997 because of cardiovascular side effects, also reduce food intake in human studies. *meta*-Chlorophenylpiperazine, a direct serotonin agonist, reduces food intake by 28% in women and 20% in men (Walsh et al., 1994). Another serotonergic drug, sumatriptan, which acts on the $5\text{-}HT_{1B/1D}$ receptor, also reduced food intake in human subjects (Boeles et al., 1997). Because of the robust effects of agonists toward the $5\text{-}HT_{2C}$ receptors in suppressing food intake, a number of new agents are now under development.

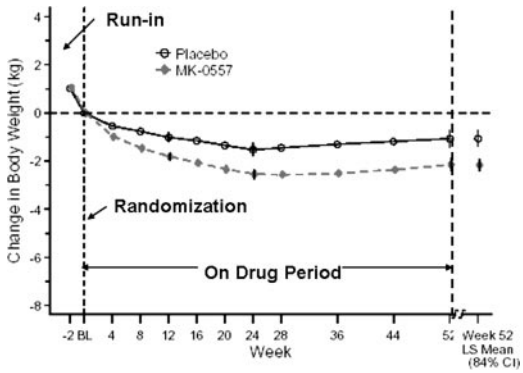

FIG. 16. Effect of an NPY antagonist on body weight in a 1-year randomized, placebo-controlled trial. Adapted from Erondu et al. (2006).

Only one of these, described below, has advanced to formal clinical trials

2. Clinical Studies. The results of a 12-week phase II dose-ranging study of lorcaserin (APD356) have been presented (Smith et al., 2006). A total of 459 male and female subjects with a BMI between 29 and 46 kg/m^2 with an average weight of 100 kg were enrolled in a randomized, double-blind, controlled trial comparing placebo against 10 and 15 mg given once daily and 10 mg given twice daily (20 mg/day). Over the 12 weeks of the trial, the placebo group gained +0.32 kg (n = 88 completers) compared with −1.8 kg in the 10-mg/day dose given once daily (n = 86 completers), −2.6 kg in the 15-mg/day dose (n = 82 completers), and −3.6 kg in the 10-mg-twice-daily dose (20 mg total) (n = 77 completers). Side effects that were higher in the active treatment groups than the placebo group were headache, nausea, dizziness, vomiting, and dry mouth. No cardiac valvular changes were noted.

D. Peptide $YY_{3\text{-}36}$

1. Mechanism of Action. $PYY_{3\text{-}36}$ is a hormone produced by the L-cells in the gastrointestinal tract and is secreted in proportion to the caloric content of a meal. $PYY_{3\text{-}36}$ levels are lower after fasting and after a meal in overweight subjects compared with lean subjects. Development of a nasal spray formulation for $PYY_{3\text{-}36}$ has undergone a phase I clinical trial. Based on the review of this trial Merck severed its commercial relationship with Nastech Pharmaceutical Company on March 1, 2006. Nastech, the developer of the nasal formulation, plans to continue developing this product.

2. Clinical Studies. Caloric intake at a lunch buffet was reduced by 30% in 12 obese subjects and by 29% in 12 lean subjects after 2 h of $PYY_{3\text{-}36}$ infused i.v. (Batterham et al., 2003). These findings were confirmed by another group in normal weight subjects. Food intake was reduced by 35% during an i.v. infusion of $PYY_{3\text{-}36}$ (Degen et al., 2005). Thrice daily nasal administration over 6 days was well tolerated and reduced caloric intake by ~30% while giving a 0.6-kg weight loss (Brandt et al., 2004).

E. Oxyntomodulin

1. Mechanism of Action. Oxyntomodulin is a gastrointestinal peptide produced in the L-cells of the intestine and is released in response to food. Animals injected with oxyntomodulin have a reduction in body fat and food intake.

2. Clinical Studies. In a short 4-week clinical study, oxyntomodulin was reported to reduce food intake by 19.3% compared with a placebo infusion (Fig, 17). In this 4-week randomized, double-blind, placebo-controlled trial, overweight volunteers injected themselves with oxyntomodulin or placebo s.c. 3 times a day 30 min before meals. Body weight was reduced -2.3 ± 0.4 kg in the group receiving oxyntomodulin compared with -0.5 ± 0.5 kg in the placebo group. Leptin decreased

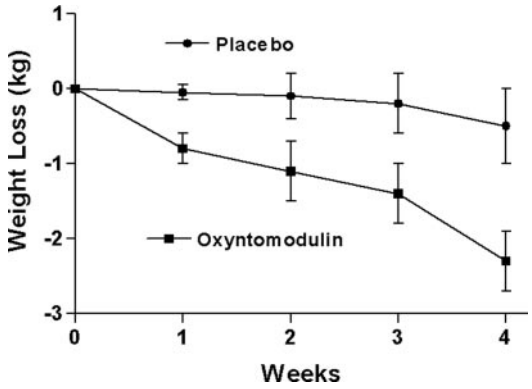

FIG. 17. Effect of oxyntomodulin on body weight in a 4-week trial. Copyright © 2005 American Diabetes Association. From Diabetes®, vol. 54, 2005; 2390–2395. Reprinted with permission from *The American Diabetes Association.*

and adiponectin increased in the group receiving oxyntomodulin. Energy intake in the treated group decreased by 170 ± 37 kcal (25 ± 5%) at the beginning study meal and by 250 ± 63 kcal (35 ± 9%) at the final meal (Wynne et al., 2005).

F. Pancreatic Lipase Inhibitor

1. Mechanism of Action. Cetilistat is a lipase inhibitor. In a 5-day trial of cetilistat (ATL-962) in 90 normal volunteers housed on an inpatient unit, there was a 3- to 7-fold increase in fecal fat that was dose-dependent. Only 11% of subjects had more than one oily stool, leading to the suggestion that this lipase inhibitor may have fewer gastrointestinal adverse events than orlistat (Dunk et al., 2002).

2. Clinical Studies. In a 12-week clinical trial, 612 obese diabetic subjects were randomized to 40, 80, or 120 mg of cetilistat, 120 mg of orlistat, or placebo given three times a day. Weight loss was −2.9, −3.9, −4.3, −3.8 kg, and −2.9 kg, respectively. The prevalence of gastrointestinal side effects was 11.6, 1.7, and 4% in the orlistat, 120 mg of cetilistat, and placebo groups, respectively (Kopelman et al., 2006).

G. Cholecystokinin

Cholecystokinin decreases food intake by causing subjects to stop eating sooner (Pi-Sunyer et al., 1982). Although the relationship between cholecystokinin and satiety has been known for many years, development as a weight loss agent has been slow due to concerns about pancreatitis. Because the human pancreas has no cholecystokinin-A receptors, an orally active compound that is a selective agonist of the cholecystokinin-A receptor has been evaluated in clinical trials, but GlaxoSmithKline issued a press release in 2005 announcing discontinuation of their program in this area.

H. Combination of Bupropion and Naltrexone (Contrave)

The combination of naltrexone and bupropion (Contrave) is being developed for the treatment of obesity. Naltrexone is approved for the treatment of alcoholism. Naltrexone does not give significant weight loss alone, but by inhibiting a μ opioid receptor on the POMC neurons, it releases these neurons from μ opioid inhibition, augmenting POMC release and the weight loss effect of bupropion. A proof of concept trial with 50 mg/day of naltrexone and 300 mg of bupropion was reported in abstract form (Greenway et al., 2006a). This 6-month study in 200 subjects gave initial body weight losses of −3.8, −2.2, −0.9, and −6.6% in the bupropion, naltrexone, placebo, and bupropion-naltrexone groups, respectively ($P < 0.02$, $P < 0.001$, and $P < 0.001$, compared with bupropion-naltrexone). Nausea, the major adverse event (40%), was driven by naltrexone and led to discontinuations in 12% of participants. Dose modification may increase efficacy and improve tolerability of this combination.

I. Combination of Bupropion and Zonisamide (Empatic)

The combination of bupropion and zonisamide (Empatic) is being developed for the treatment of obesity. A proof of concept trial with placebo, 300 mg/day of bupropion, 400 mg of zonisamide, and the combination was reported in abstract form (Greenway et al., 2006b). This 6-month study in 220 subjects gave initial body weight losses of −0.4, −3.6, −6.6, and −9.2% in the placebo, bupropion, zonisamide, and bupropion-zonisamide groups, respectively. The bupropion-zonisamide group lost 12% of initial body weight at 48 weeks. Adverse events with prevalence >10% included insomnia, nausea, fatigue, upper respiratory infection, headache, and anxiety. Tolerability may be improved by dosage modification.

J. Combination of Topiramate and Phentermine (Qnexa)

A combination of phentermine and topiramate (Qnexa) is being developed for the treatment of obesity (Gadde et al., 2006). A 6-month study in 200 subjects gave an −11.4-kg weight loss in the phentermine-topiramate group and a −2.3-kg weight loss in the placebo group. More than half of the phentermine-topiramate subjects lost 10% of their initial body weight. The drop-out rate in the phentermine-topiramate group was 8% compared with 38% in the placebo group (2006).

VII. Drugs in the Early Phases of Development

A. Melanin-Concentrating Hormone Receptor-1 Antagonist

Melanin-concentrating hormone and α-melanocyte-stimulating hormone have opposite effects on skin coloration in fish. Melanin-concentrating hormone blocks the effects of α-melanocyte-stimulating hormone on food

intake when both are injected into the cerebral ventricles of rats (Ludwig et al., 1998). Melanin-concentrating hormone has two receptors MCH-1 and MCH-2. Mice without the MCH-1 receptor have increased activity, increased temperature, and increased sympathetic tone (Astrand et al., 2004). Overexpression of the MCH-1 receptor and chronic infusion of an MCH-1 agonist cause enhanced feeding, caloric efficiency, and weight gain, whereas an MCH-1 antagonist reduces food intake and body weight gain without an effect on lean tissue (Shearman et al., 2003). MCH-1 antagonists reduce food intake by decreasing meal size and also act as antidepressants and anxiolytics (Borowsky et al., 2002; Kowalski et al., 2004). An orally active MCH-1 receptor antagonist that has good plasma levels and central nervous system exposure induced weight loss in obese mice with chronic treatment (Souers et al., 2005). A number of other MCH-1 antagonists reduce food intake and body weight in experimental animals (Handlon and Zhou, 2006). No human studies have been reported.

B. Histamine-3 Receptor Antagonists

Histamine and its receptors can affect food intake. Among the antipsychotic drugs that produce weight gain, binding to the H1 receptor is higher than with any other monoamine receptor and histamine reduces food intake by acting on this receptor (Kroeze et al., 2003). The search for drugs that can modulate food intake through the histamine system has focused on the histamine H3 receptor, which is an autoreceptor; that is, activation of this receptor inhibits histamine release, whereas blockade of the receptor increases histamine release. Both imidazole and nonimidazole antagonists of the H3 receptor have been published and shown to reduce food intake and body weight gain in experimental animals (Leurs et al., 2005; Nilsson, 2006).

Betahistine was approved for the treatment of vertigo in the United States when only demonstration of safety was required but was removed from the market in the early 1970s after the U.S. Food and Drug Administration began requiring proof of efficacy. Betahistine has continued to be used and well tolerated in other countries to the present day and is now understood to stimulate the histamine-1 receptor through antagonism at the histamine-3 receptor (Tighilet et al., 2002). Betahistine decreases food intake in rats in a dose-dependent manner, both orally and parenterally (Szelag et al., 2001). Water intake was stimulated and food intake was suppressed by betahistine given parenterally to pygmy goats (Rossi et al., 1999). Betahistine was given to three human subjects at 48 mg t.i.d. in conjunction with 10 mg/day of olanzapine in the treatment of new-onset schizophrenia. There was a 3.1 ± 0.9-kg weight gain in the first 2 weeks, but no subsequent weight gain over the next month of treatment, and betahistine did not affect the antipsychotic effect of olanzapine (Poyurovsky et al., 2004). Betahistine has also been shown to improve arteriosclerotic dementia (Pathy et al., 1977; Seipel et al., 1977).

C. Ghrelin Antagonists

Ghrelin is a small peptide synthesized in the stomach. Its active form contains an octanoate on the third amino acid. The level rises with fasting and declines after eating, suggesting that it may be a satiety signal. Chronic administration produces hyperphagia and weight gain in animals. Moreover, obese subjects have lower levels than normal-weight individuals.

Ghrelin acts at the growth hormone secretogogue receptor to produce its effects. A group of growth hormone-stimulating peptides that also act on this growth hormone secretogogue receptor are known to increase food intake in human subjects (Laferrere et al., 2005). Antagonists to this receptor might thus be useful drugs for treating overweight patients; this theory is supported by suppression of food intake and attenuated weight regain in diet-induced obese mice treated with such drugs.

D. Angiogenesis Antagonists and Fat Cell Antibodies

Formation of an enlarging fat organ requires new blood vessels, and the concept of inhibiting the growth of these vessels and thus showing fat cell growth is an intriguing possibility. Experimental studies in mice have shown that an antagonist of angiogenesis can inhibit fat cell development in *ob*/*ob* mice (Rupnick et al., 2002; Brakenhielm et al., 2004). The discovery that fumagillin, isolated from the fungus *Aspergillus fumigatus*, inhibits blood vessel growth has provided a platform for development of new drugs. Fumagillol has provided one derivative, TNP-470, that has been tested by Rupnick et al. (2002). This study showed that TNP-470 reduces body weight and slightly decreases food intake in animal models of obesity.

VIII. Drugs and Herbal Medications No Longer under Investigation or Withdrawn

A. Ephedra

Ephedrine combined with methylxanthines were used in the treatment of asthma for decades. A physician in Denmark noted weight loss in his patients taking this combination drug for asthma. The combination of 200 mg of caffeine and 20 mg of ephedrine given three times a day was subsequently approved as a prescription medication for overweight in Denmark, where it had commercial success for more than a decade (Greenway, 2001). In 1994, legislation in the United States declared ephedra and caffeine to be foods, eligible to be sold as dietary herbal supplements. The use of this combination as an unregulated dietary supplement for the treatment of overweight was accompanied by reports of cardiovascular and neuropsychiatric adverse events leading to the FDA declaring ephedra, the herbal form of ephedrine, as an adulterant (Shekelle et al., 2003). Recently, courts in

the United States have overturned the FDA decision to withdraw ephedra from the herbal market, at least in regard to ephedra doses of ≤10 mg, but the implications that this legal decision may have on the availability of ephedra in the herbal dietary supplement market remains to be determined. A recent small-size, 9-month, randomized, placebo-controlled trial (Hackman et al., 2006) showed that subjects taking an herbal preparation containing ephedra, green tea extract, guarana (caffeine source), *Garcinia cambogia* and other botanicals, plus a high-potency multivitamin/mineral pill plus a capsule with *n*-3 fatty acids lost −7.18 kg in 9 months compared with −2.25 kg in the placebo group. This result suggests that the market for ephedra combinations with other botanicals may still be alive.

B. β_3-Adrenergic Agonists

In the early 1980s, the β_3-adrenergic receptor was identified and shown in animals to increase lipolysis, fat oxidation, energy expenditure and insulin action when stimulated. Selective β-adrenergic agonists based on the rodent β_3-adrenergic receptor were not selective in humans, and the human β_3-adrenergic receptor was subsequently cloned and found to be only 60% homologous with that of rodents (de Souza and Burkey, 2001). A β_3-adrenergic agonist selective for the human β_3-receptor, L-796568, increased lipolysis and energy expenditure when given as a single 1000-mg dose to overweight men without significant stimulation of the β_2-adrenergic receptor (van Baak et al., 2002). A 28-day study with the same compound at 375 mg/day versus a placebo in obese men gave no significant increase in energy expenditure, reduction in respiratory quotient, or changes in glucose tolerance. There was a significant reduction of triglycerides, however. This lack of a chronic effect was interpreted as either a lack of recruitment of β_3-responsive tissues, a down-regulation of β_3-receptors, or both (Larsen et al., 2002). Thus, despite encouraging results from rodents, human trials of selective β_3-agonists have been disappointing.

C. Bromocriptine

Hibernating and migratory animals change their ability to store and burn fat on the basis of circadian rhythms, and these circadian rhythms are controlled by prolactin secretion. It has been postulated that overweight and diabetic individuals have abnormal circadian rhythms. These abnormal rhythms favor fat storage and insulin resistance. Rapid-release bromocriptine (Ergocet), given at 8 A.M, has been postulated to reverse this abnormal circadian rhythm and effectively treat diabetes and overweight. An uncontrolled trial of quick-release bromocriptine given orally for 8 weeks significantly decreased 24-h plasma glucose, free fatty acid, and triglyceride levels from baseline (Kamath et al., 1997). This was followed by a controlled trial in which 22 diabetic subjects were randomized to quick-release bromocriptine or placebo. Hemoglobin A_{1c} fell from 8.7to 8.1% in the bromocriptine group and rose from 8.5 to 9.1% in the placebo group, a statistically significant difference (Pijl et al., 2000). In an uncontrolled trial, 33 overweight postmenopausal women reduced their body fat by 11.7% measured by skinfold thickness over 6 weeks of treatment with quick-release bromocriptine (Meier et al., 1992). This was followed by a controlled trial in which 17 overweight subjects were randomized to rapid-release bromocriptine (1.6–2.4 mg/day) or a placebo for 18 weeks. The bromocriptine group lost significantly more weight (6.3 kg versus 0.9 kg) and more fat as measured by skinfold thicknesses (5.4 kg versus 1.5 kg) (Cincotta and Meier, 1996). The company developing Ergocet received an approvable determination by the FDA for quick-release bromocriptine to treat diabetes but was asked to do additional safety studies. These studies were never performed, and the obesity development program proceeded no further.

D. Ecopipam

Ecopipam is a dopamine 1 and 5 receptor antagonist that was originally studied for the treatment of cocaine addiction (Nann-Vernotica et al., 2001). Ecopipam was in development as a drug to treat overweight, but its development was terminated (Bays and Dujovne, 2002).

There were four randomized, double-blind, multicenter trials comparing ecopipam (n = 1667) and placebo (n = 1118) in obese subjects including type 2 diabetic subjects. Subjects received 10, 30, or 100 mg of oral ecopipam q.d. for 12 weeks (phase 2) or 50 or 100 mg q.d. for 52 weeks (phase 3). In the phase 3 studies, 100 mg of ecopipam produced a 3.1 to 4.3% greater weight loss than placebo at 52 weeks. Phase 3 studies were discontinued because of unexpected psychiatric adverse events (ecopipam 31% versus placebo 15%) including depression, anxiety, and suicidal ideation (Astrup et al., 2007).

E. Axokine

Axokine is a derivative of ciliary neurotrophic factor that, like leptin, acts through the STAT signaling pathway in the brain (Anderson et al., 2003). Axokine has been tested in two phase II studies, one in overweight patients and one in diabetic patients, and a phase III study in overweight patients. The first multicenter 12-week phase II study randomized 170 obese subjects with a BMI between 35 and 50 kg/m^2. The optimal dose was 1 μg/kg, and this group lost −4.6 kg compared with a weight gain of +0.6 kg in the placebo group (Ettinger et al., 2003). The second 12-week phase II study randomized 107 obese type 2 diabetic subjects with a BMI between 35 and 50 kg/m^2 (http://www.regeneron.com/company/press_detail.asp?v_c_id=170). Those subjects treated with the 1.0-μg/kg dose of axokine lost −3.2 kg compared with −1.2 kg in the placebo group ($P < 0.01$).

The 1-year phase III trial with a 1-year open label extension randomized 501 subjects to placebo and 1467

subjects to axokine at a dose of 1 μg/kg/day (http://www.regeneron.com). Subjects had a BMI between 30 and 55 kg/m^2, if their overweight was uncomplicated, or between 27 and 55 kg/m^2, if their overweight was complicated by hypertension or dyslipidemia. At the end of 1 year, the axokine group lost −3.6 kg compared with −2.0 kg in the placebo group ($P < 0.001$), a difference that does not meet the FDA efficacy criteria for approval. The most common adverse events were mild and included injection site reactions, nausea, and cough. The most concerning finding, however, was that two-thirds of those receiving axokine developed antibodies after 3 months that limited weight loss, and there was no way to prospectively predict those who would develop antibodies. Development of axokine has been terminated.

IX. Over-the-Counter Medications

A. Orlistat

Orlistat at a dose of 60 mg/day is an over-the-counter preparation for overweight individuals. This preparation has been approved by the FDA and is marketed under the trade name Alli to be used by overweight adults for up to 6 months along with a weight loss program.

B. Phenylpropanolamine

Short-term weight loss with phenylpropanolamine was similar to the short-term weight losses seen with prescription drugs for overweight (Greenway, 1992). The longest study of phenylpropanolamine lasted 20 weeks and produced a −5.1-kg weight loss in the drug group compared with −0.4-kg weight loss in the placebo group, which was >5% compared with placebo (Schteingart, 1992). Although phenylpropanolamine had a long history of safety in clinical trials dating to the 1930s, it was taken off the market because of an association with hemorrhagic stroke in women (Kernan et al., 2000).

X. Herbal Products, Functional Foods, and Nutriceuticals

Two recent articles have examined randomized clinical trials for complementary therapies for reducing body weight (Dwyer et al., 2005; Pittler and Ernst, 2005).

A. Interventions Requiring Special Training

1. Acupuncture/Acupressure. Acupuncture consists of placing needles at key points controlling neural connections for relief of pain and other clinical purposes. Pittler and Ernst (2005) identified four randomized, controlled trials in which sham treatments were used. Two of the randomized trials of acupuncture reported a reduction in hunger, whereas two others showed no differences in body weight. Overall, the evidence does not support a specific acupuncture procedure that works.

2. Homeopathy. Two different preparations have been used in homeopathic doses to treat overweight, and they were reflected in two randomized, controlled trials. *Helianthus tuberoses* D1 was investigated for 3 months in one trial in which those receiving the active ingredient lost −7.1 kg, which was significantly more than in the placebo group. In a second trial, a single dose of Thyroidinum 30cH was given to fasting patients, but it was no more effective than placebo.

3. Hypnotherapy. Hyponotherapy has been examined in six randomized, controlled trials in which hypnotherapy plus cognitive behavior therapy was compared with cognitive behavior therapy alone. The addition of hyponotherapy to cognitive behavior therapy adds a small, but significant, weight loss to the cognitive behavior therapy (Pittler and Ernst, 2005).

B. Minerals and Metabolites

1. Chromium Picolinate. Chromium is a trace mineral and a cofactor to insulin. It has been claimed that chromium can cause weight loss and fat loss while increasing lean body mass. A recent meta-analysis of 10 double-blind, randomized, controlled trials in participants with a BMI between 28 and 33 kg/m^2, showed a statistically significant weight loss of 1.1 to 1.2 kg over a 6- to 14-week treatment period. There were no adverse events, but the authors pointed out that this weight loss, although statistically significant, was not clinically significant (Pittler and Ernst, 2004). These data have to be interpreted cautiously, because they rely heavily on one robust study. Cefalu et al. (2002) in a review of the field have shown that chromium picolinate may have a significant effect in preventing weight regain. Dwyer et al. (2005) concluded that there is little evidence of benefit and few or no adverse events.

2. Hydroxymethyl Butyrate. β-Hydroxy-β-methylbutyrate is a metabolite of leucine. It acts in vivo to inhibit the breakdown of protein. In a literature review, Pittler and Ernst (2005) found two randomized, controlled trials that reported significant differences in fat mass reduction and at least a trend toward an increase in lean body mass. Further studies are clearly needed.

3. Pyruvate. Pyruvate is an intermediary in the metabolism of glucose and also serves as a hydrogen shuttle between liver and muscle. It has been suggested to improve exercise performance and body composition at 7 to 20% of dietary calories but is sold as a dietary herbal supplement for obesity at a dose of ~3 g/day. Pittler and Ernst (2005) identified two randomized, controlled trials that included subjects with a BMI of ≥25 kg/m^2. There were no significant effects on body weight reduction compared with placebo. They concluded that the case for pyruvate as a dietary herbal supplement is weak.

4. Conjugated Linoleic Acid. The word "conjugated" in linoleic acid refers to the position of the double bond between carbons 9 and 11 or 10 and 12. There are

differences in effects of each of the isomeric combinations. In an analysis of 13 randomized, controlled trials lasting ≤6 months Larsen et al. (2003) reported that there was little evidence that conjugated linoleic acid produced weight loss in humans, although one report suggested that it lowers body fat without an effect on body weight (Riserus et al., 2004). There is also concern about liver toxicity from the *trans*-10, *cis*-12 isomer and the induction of insulin resistance. Dwyer et al. (2005) concluded that there is little evidence of benefit.

5. Calcium. Nearly 20 years ago McCarron et al. (1984) reported that there was a negative relationship between body mass index and dietary calcium intake in the data collected by the National Center for Health Statistics. More recently Zemel et al. (2000) found that there was a strong inverse relationship between calcium intake and the risk of being in the highest quartile of body mass index. These studies have prompted a reevaluation of studies measuring calcium intake or giving calcium orally.

The relationship of calcium and body weight is problematic, however, because a patent was issued for the effects of dairy products for producing weight loss to one of the proponents of this approach. Such a relationship in which monetary gain is associated with publication of positive studies raises concerns when one is reading the published studies. Moreover, there is inconsistency in both the animal and human studies.

In one small clinical trial, increasing dietary intake of calcium by adding 800 mg/day of supplemental calcium to a diet containing 400 to 500 mg/day was claimed to augment weight loss and fat loss on reducing diets (Zemel et al., 2004). In two small studies in African-American adults Zemel et al. (2005b) claimed that substitution of calcium-rich foods in isocaloric diets reduced adiposity and improved metabolic profiles during a 24 week trial. In another small study Zemel et al. (2005a) randomized 34 subjects to receive a control calcium diet with 400 to 500 mg/day ($n = 16$) or a yogurt-supplemented diet ($n = 18$) for 12 weeks. In this small, short-duration study, fat loss was greater with the yogurt diet (−4.43 kg) than with the control diet (−2.75 kg). On the basis of these data, they claim that yogurt enhances central fat loss. In a large multicenter trial that enrolled nearly 100 subjects, the same authors claimed that a hypocaloric diet with calcium supplemented to the level of 1400 mg/day did not significantly improve weight loss or body composition compared with a diet with lower calcium intake (600 mg/day), whereas a diet with three servings per day of dairy products augmented weight and fat loss (Zemel et al., 2005b).

Increasing supplemental calcium from 0 to nearly 2000 mg/day was associated with a reduction in BMI of ~5 BMI units (Davies et al., 2000). These data might suggest that low calcium intake was playing a role in the current epidemic of overweight. However, three controlled clinical trials have failed to show an effect of calcium on weight loss, leaving the issue in limbo (Shapses et al., 2001, 2004; Barr, 2003). Dwyer et al. (2005) concluded that the evidence of benefit is equivocal and limited to small trials, but there are no major concerns regarding adverse events.

C. Herbal Dietary Supplements

1. Ephedra sinica. *E. sinica* is an evergreen that grows in central Asia, and its principal ingredient is ephedrine (see also Section VIII.A.). Ephedrine with caffeine has been shown to produce weight loss in randomized, placebo-controlled clinical trials (Astrup et al., 1992). The ephedra alkaloids from ma huang contain ephedrine, and three randomized placebo-controlled clinical trials, one for 2 months, one for 3 months, and one for 6 months showed significantly greater weight loss than with placebo (Boozer et al., 2001). Ephedra-containing herbal preparations were removed from the market by the U.S. Food and Drug Administration in April 2004 because of alleged harmful cardiovascular side effects (Shekelle et al., 2003), but this act, as stated above, has recently been reversed.

2. Green Tea Extract. Green tea extract is a common ingredient in dietary herbal supplements for weight loss, and it contains catechins and caffeine. Green tea catechins such as epigallocatechin gallate inhibit catechol-*O*-methyl transferase, the enzyme that degrades norepinephrine (Borchardt and Huber, 1975). In vitro brown fat cell experiments show catechins and caffeine to be synergistic in stimulating thermogenesis (Dulloo et al., 2000). Subjects given green tea capsules three times a day with a total of 150 mg of caffeine and 375 mg of catechins of which 270 mg was epigallocatechin gallate had a 4.5% increase in 24-h metabolic rate in a metabolic chamber and a 3.2% increase with caffeine alone compared with placebo. Fat oxidation was increased, and green tea extract increased 24-h metabolic rate 328 kJ/day (~80 kcal/day) (Dulloo et al., 1999). Another study by Belza and Jessen (2005) showed a statistically significant 200 kJ/day increase in metabolic rate in a metabolic chamber study with a combination of capsaicin, green tea extract, tyrosine, and calcium.

Clinical trials for weight loss are much less encouraging. Chantre and Lairon (2002) reported a 4.6% weight loss over 12 weeks in an open-label study, 2002), but a placebo-controlled study of green tea extract in subjects with polycystic ovarian disease gave a 2.4% weight loss over 3 months that was not significantly greater than the loss with placebo, and there were no improvements in glucose or lipid metabolism (Chan et al., 2006). Kovacs et al. (2004) found that green tea extract was no better than placebo in maintaining a 7.5% weight loss over 13 weeks. This result was confirmed in a similar weight maintenance study by Westerterp et al. (2005). Thus, green tea extract seems to have little potential as a treatment for obesity.

3. Garcinia cambogia. *G. cambogia* contains hydroxycitric acid, an inhibitor of citrate cleavage enzyme (ATP-citrate lyase) that inhibits fatty acid synthesis from carbohydrate. Hydroxycitrate was studied by Hoffmann-LaRoche in the 1970s and was shown to reduce food intake and cause weight loss in rodents (Sullivan and Triscari, 1977). Although there have been reports of successful weight loss with small studies in humans, some of which included other herbs, the largest and best designed placebo-controlled study demonstrated no difference in weight loss compared with a placebo (Heymsfield et al., 1998; Pittler and Ernst, 2004). Thus, there is no evidence for efficacy.

4. Yohimbine from Pausinystalia yohimbe. Yohimbine is an α_2-adrenergic receptor antagonist that is isolated from *P. yohimbe*. The three randomized clinical trials that Pittler and Ernst (2005) identified give conflicting results as to whether there is significant weight loss with this plant extract compared with placebo.

5. Hoodia. *Hoodia gordonii* is a cactus that grows in Africa. It has been eaten by Bushmen to decrease appetite and thirst on long treks across the desert. The active ingredient is a steroidal glycoside called P57AS3 or just P57. P57 injected into the third ventricle of animals increases the ATP content of hypothalamic tissue by 50 to 150% and decreases food intake by 40 to 60% over 24 h (MacLean and Luo, 2004). A double-blind 15-day trial in which 19 overweight males were randomized to P57 or placebo has been put on a Web site (http://www.phytopharm.co.uk/news/newsreleases/?page=6&id=1749). Nine subjects in each group completed the study. There was a statistically significant decrease in calorie intake and body fat and no serious adverse events. Because Hoodia is a rare cactus in the wild and cultivation is difficult, it is not clear what the dietary herbal supplements claiming to contain Hoodia actually contain or if they are effective in causing weight loss.

6. Citrus aurantium *(Bitter Orange).* Since the withdrawal of ephedra from the dietary herbal supplement market, manufacturers of dietary herbal supplements for weight loss have turned to *C. aurantium*, which contains phenylephrine. A recent systematic review found only one randomized, placebo-controlled trial involving 20 subjects treated with *C. aurantium* for 6 weeks. This trial demonstrated no statistically significant benefit for weight loss (Bent et al., 2004). Since that review, there was a report of two small studies, one with eight subjects randomized to *C. aurantium* or placebo and the other an open-label study with 20 subjects. The first showed weight gain in the *C. aurantium* group and the second showed only an 0.8-kg weight loss, which was not statistically or clinically significant (Greenway et al., 2006c). There have been reports of cardiovascular events associated with the use of *C. aurantium*, including a prolonged QT interval with syncope and an acute myocardial infarction (Nasir et al., 2004; Nykamp et al., 2004). Thus, there is no evidence for efficacy of *C. aurantium* in the treatment of overweight, but concern does exist regarding its safety. Dwyer et al. (2005) concluded that there is no adequate evidence for efficacy and that there are safety concerns

7. Ayurvedic Preparations. Ayurvedic medicine is the traditional medicine of India. Ayurvedic herbal preparations containing *Triphala guggul* have been assessed in one randomized clinical trial (Pittler and Ernst, 2005). Patients in the treated group lost between 7.9 and 8.2 kg, which was significantly greater than for placebo (Paranjpe et al., 1990).

D. Fibers

The possibility that fiber might be useful in maintaining lower weight comes from epidemiological studies. A recent reexamination of data from the Seven Countries Study has shown that the fiber intake within each of the participating countries was inversely related to the body weight. Men eating more fiber had lower body weight. Epidemiological data suggest that countries in which individuals have higher fiber consumption have a lower prevalence of overweight (Kromhout et al., 2001). Low fiber intake may also be related to the development of heart disease (Wolk et al., 1999) and diabetes (Salmeron et al., 1997). Fiber supplements increase satiety when calories are held constant, and 14 g of fiber per day decreases food intake by 10% resulting in ~2.4 kg of weight loss in the obese (Howarth et al., 2001).

1. Chitosan. Chitosan or acetylated chitin is a dietary fiber derived from crustaceans that has been advocated as a weight loss agent. A recent systematic review of the randomized clinical trials of chitosan concluded, on the basis of 14 trials of >4 weeks involving 1071 subjects, that chitosan produced a statistically significantly greater 1.7-kg weight loss compared with placebo (Mhurchu et al., 2005). This degree of weight loss falls far short of the 5 kg felt to be clinically significant, however. Dwyer et al. (2005) concluded that there is little evidence of benefit and some adverse gastrointestinal symptoms.

2. Glucomannan. Glucomannan is derived from the root of the *Amorphophallus konjac* plant. Its chemical structure is similar to that of galactomannan in guar gum. They are both polysaccharide chains of glucose and mannose and serve as water-soluble fibers. In one randomized, controlled trial identified by Pittler and Ernst (2005), the subjects were ≥20% overweight, and those in the group receiving glucomannan lost more weight than the placebo group.

3. Guar Gum. Guar gum is an extract from *Cyamopsis tetragonolobus.* It is the most widely studied of the compounds in this group with 20 randomized placebo-controlled trials. In a meta-analysis of 11 of these trials, the data showed that guar gum is no more effective than placebo in treating obesity (Pittler and Ernst, 2005).

4. Plantago *psyllium.* The psyllium extract from the seeds of this plant is a water soluble fiber. In one randomized, placebo-controlled trial identified by Pittler and Ernst (2005) there was no significant change in body weight in either the treatment or placebo group.

XI. Conclusions

Although the drugs presently available for the treatment of overweight patients are few in number and limited in efficacy, the pipeline for drug development is very rich. Because drug development is more sophisticated today than in the past, we anticipate that the development of safe and effective drugs for the treatment of overweight will proceed at a more rapid pace than was the case for other chronic diseases that presently have safe and effective medications, such as hypertension and diabetes.

REFERENCES

Anderson JW, Greenway FL, Fujioka K, Gadde KM, McKenney J, and O'Neil PM (2002) Bupropion SR enhances weight loss: a 48-week double-blind, placebo-controlled trial. *Obes Res* **10:**633–641.

Anderson KD, Lambert PD, Corcoran TL, Murray JD, Thabet KE, Yancopoulos GD, and Wiegand SJ (2003) Activation of the hypothalamic arcuate nucleus predicts the anorectic actions of ciliary neurotrophic factor and leptin in intact and gold thioglucose-lesioned mice. *J Neuroendocrinol* **15:**649–660.

Anonymous (1996) Dexfenfluramine for obesity. *Med Lett Drugs Ther* **38:**64–65.

Apfelbaum M, Vague P, Ziegler O, Hanotin C, Thomas F, and Leutenegger E (1999) Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the efficacy and tolerability of sibutramine. *Am J Med* **106:**179–184.

Astrand A, Bohlooly YM, Larsdotter S, Mahlapuu M, Andersen H, Tornell J, Ohlsson C, Snaith M, and Morgan DG (2004) Mice lacking melanin-concentrating hormone receptor 1 demonstrate increased heart rate associated with altered autonomic activity. *Am J Physiol* **287:**R749–R758.

Astrup A, Breum L, Toubro S, Hein P, and Quaade F (1992) The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy restricted diet: a double blind trial. *Int J Obes Relat Metab Disord* **16:**269–277.

Astrup A, Caterson I, Zelissen P, Guy-Grand B, Carruba M, Levy B, Sun X, and Fitchet M (2004) Topiramate: long-term maintenance of weight loss induced by a low-calorie diet in obese subjects. *Obes Res* **12:**1658–1669.

Astrup A, Greenway FL, Ling W, Pedicone L, Lachowicz J, Strader CD, and Kwan R (2007) Randomized controlled trials of the D1/D5 antagonist ecopipam for weight loss in obese subjects. *Obes Res,* in press.

Astrup A and Toubro S (2004) Topiramate: a new potential pharmacological treatment for obesity. *Obes Res* **12(Suppl):**167S–173S.

Avenell A, Brown TJ, McGee MA, Campbell MK, Grant AM, Broom J, Jung RT, and Smith WC (2004) What interventions should we add to weight reducing diets in adults with obesity? A systematic review of randomized controlled trials of adding drug therapy, exercise, behavior therapy or combinations of these interventions. *J Hum Nutr Diet* **17:**293–316.

Aydin N, Topsever P, Kaya A, Karasakal M, Duman C, and Dagar A (2004) Orlistat, sibutramine, or combination therapy: which performs better on waist circumference in relation with body mass index in obese patients? *Tohoku J Exp Med* **202:**173–180.

Barkeling B, Elfhag K, Rooth P, and Rossner S (2003) Short-term effects of sibutramine (Reductil) on appetite and eating behavior and the long-term therapeutic outcome. *Int J Obes Relat Metab Disord* **27:**693–700.

Barr SI (2003) Increased dairy product or calcium intake: is body weight or composition affected in humans? *J Nutr* **133:**245S–248S.

Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, Ghatei MA, and Bloom SR (2003) Inhibition of food intake in obese subjects by peptide YY3–36. *N Engl J Med* **349:**941–948.

Bays H and Dujovne C (2002) Anti-obesity drug development. *Expert Opin Investig Drugs* **11:**1189–1204.

Belza A and Jessen AB (2005) Bioactive food stimulants of sympathetic activity: effect on 24-h energy expenditure and fat oxidation. *Eur J Clin Nutr* **59:**733–741.

Ben-Menachem E, Axelsen M, Johanson EH, Stagge A, and Smith U (2003) Predictors of weight loss in adults with topiramate-treated epilepsy. *Obes Res* **11:**556–562.

Bensaid M, Gary-Bobo M, Esclangon A, Maffrand JP, Le Fur G, Oury-Donat F, and Soubrie P (2003) The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. *Mol Pharmacol* **63:**908–914.

Bent S, Padula A, and Neuhaus J (2004) Safety and efficacy of citrus aurantium for weight loss. *Am J Cardiol* **94:**1359–1361.

Berkowitz R, Fujioka K, Daniels S, Hoppin A, Owen S, Perry A, Sothern M, Renz C, Pimer M, Walch J, et al. (2006) Weight loss in adolescents treated with sibutramine: a randomized, placebo-controlled trial. *Ann Intern Med* **145:**81–90.

Berkowitz RI, Wadden TA, Tershakovec AM, and Cronquist JL (2003) Behavior therapy and sibutramine for the treatment of adolescent obesity: a randomized controlled trial. *J Am Med Assoc* **289:**1805–1812.

Blonde L, Klein EJ, Han J, Zhang B, Mac SM, Poon TH, Taylor KL, Trautmann ME, Kim DD, and Kendall DM (2006) Interim analysis of the effects of exenatide treatment on A_{1c}, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. *Diabetes Obes Metab* **8:**436–447.

Boeles S, Williams C, Campling GM, Goodall EM, and Cowen PJ (1997) Sumatriptan decreases food intake and increases plasma growth hormone in healthy women. *Psychopharmacology* **129:**179–182.

Boozer CN, Nasser JA, Heymsfield SB, Wang V, Chen G, and Solomon JL (2001) An herbal supplement containing ma huang-guarana for weight loss: a randomized, double-blind trial. *Int J Obes Relat Metab Disord* **25:**316–324.

Borchardt RT and Huber JA (1975) Catechol *O*-methyltransferase. 5. Structure-activity relationships for inhibition by flavonoids. *J Med Chem* **18:**120–122.

Borowsky B, Durkin MM, Ogozalek K, Marzabadi MR, DeLeon J, Lagu B, Heurich R, Lichtblau H, Shaposhnik Z, Daniewska I, et al. (2002) Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist. *Nat Med* **8:**825–830.

Brakenhielm E, Cao R, Gao B, Angelin B, Cannon B, Parini P, and Cao Y (2004) Angiogenesis inhibitor TNP-470, prevents diet-induced and genetic obesity in mice. *Circ Res* **94:**1579–1588.

Brandt G, Sileno A, and Quay S (2004) Intranasal peptide YY 3–36: phase 1 dose ranging and dose sequencing studies. *Obes Res* **12(Suppl):**A28.

Bray GA (2004) Obesity is a chronic, relapsing neurochemical disease. *Int J Obes Relat Metab Disord* **28:**34–38.

Bray GA, Blackburn GL, Ferguson JM, Greenway FL, Jain AK, Mendel CM, Mendels J, Ryan DH, Schwartz SL, Scheinbaum ML, et al. (1999) Sibutramine produces dose-related weight loss. *Obes Res* **7:**189–198.

Bray GA and Gallagher TF Jr (1975) Manifestations of hypothalamic obesity in man: a comprehensive investigation of eight patients and a review of the literature. *Medicine (Baltimore)* **54:**301–330.

Bray GA and Greenway FL (1999) Current and potential drugs for treatment of obesity. *Endocr Rev* **20:**805–875.

Bray GA, Hollander P, Klein S, Kushner R, Levy B, Fitchet M, and Perry BH (2003) A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. *Obes Res* **11:**722–733.

Broom I, Wilding J, Stott P, and Myers N (2002) Randomized trial of the effect of orlistat on body weight and cardiovascular disease risk profile in obese patients: UK Multimorbidity Study. *Int J Clin Pract* **56:**494–499.

Buse JB, Henry RR, Han J, Kim DD, Fineman MS, and Baron AD (2004) Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* **27:**2628–2635.

Cangiano C, Ceci F, Cascino A, Del Ben M, Laviano A, Muscaritoli M, Antonucci F, and Rossi-Fanelli F (1992) Eating behavior and adherence to dietary prescriptions in obese adult subjects treated with 5-hydroxytryptophan. *Am J Clin Nutr* **56:**863–867.

Cangiano C, Laviano A, Del Ben M, Preziosa I, Angelico F, Cascino A, and Rossi-Fanelli F (1998) Effects of oral 5-hydroxy-tryptophan on energy intake and macronutrient selection in noninsulin dependent diabetic patients. *Int J Obes Relat Metab Disord* **22:**648–654.

Cefalu WT, Wang ZQ, Zhang XH, Baldor LC, and Russell JC (2002) Oral chromium picolinate improves carbohydrate and lipid metabolism and enhances skeletal muscle Glut-4 translocation in obese, hyperinsulinemic (JCR-LA corpulent) rats. *J Nutr* **132:**1107–1114.

Chan CC, Koo MW, Ng EH, Tang OS, Yeung WS, and Ho PC (2006) Effects of Chinese green tea on weight, and hormonal and biochemical profiles in obese patients with polycystic ovary syndrome—a randomized placebo-controlled trial. *J Soc Gynecol Investig* **13:**63–68.

Chanoine JP, Hampl S, Jensen C, Boldrin M, and Hauptman J (2005) Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *J Am Med Assoc* **293:**2873–2883.

Chantre P and Lairon D (2002) Recent findings of green tea extract AR25 (Exolise) and its activity for the treatment of obesity. *Phytomedicine* **9:**3–8.

Cincotta AH and Meier AH (1996) Bromocriptine (Ergoset) reduces body weight and improves glucose tolerance in obese subjects. *Diabetes Care* **19:**667–670.

Colman E (2005) Anorectics on trial: a half century of federal regulation of prescription appetite suppressants. *Ann Intern Med* **143:**380–385.

Damci T, Yalin S, Balci H, Osar Z, Korugan U, Ozyazar M, and Ilkova H (2004) Orlistat augments postprandial increases in glucagon-like peptide 1 in obese type 2 diabetic patients. *Diabetes Care* **27:**1077–1080.

Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, Heimburger DC, Lucas CP, Robbins DC, Chung J, et al. (1999) Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *J Am Med Assoc* **281:**235–242.

Davies KM, Heaney RP, Recker RR, Lappe JM, Barger-Lux MJ, Rafferty K, and Hinders S (2000) Calcium intake and body weight. *J Clin Endocrinol Metab* **85:**4635–4638.

de Souza CJ and Burkey BF (2001) β_3-Adrenoceptor agonists as anti-diabetic and anti-obesity drugs in humans. *Curr Pharm Des* **7:**1433–1449.

DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, and Baron AD (2005) Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* **28:**1092–1100.

Degen L, Oesch S, Casanova M, Graf S, Ketterer S, Drewe J, and Beglinger C (2005) Effect of peptide YY3–36 on food intake in humans. *Gastroenterology* **129:**1430–1436.

Despres JP, Golay A, and Sjostrom L (2005) Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* **353:**2121–2134.

Devinsky O, Vuong A, Hammer A, and Barrett PS (2000) Stable weight during lamotrigine therapy: a review of 32 studies. *Neurology* **54:**973–975.

Drent ML, Zelissen PM, Koppeschaar HP, Nieuwenhuyzen Kruseman AC, Lutterman JA, and van der Veen EA (1995) The effect of dexfenfluramine on eating habits in a Dutch ambulatory android overweight population with an overconsumption of snacks. *Int J Obes Relat Metab Disord* **19:**299–304.

Dulloo AG, Duret C, Rohrer D, Girardier L, Mensi N, Fathi M, Chantre P, and Vandermander J (1999) Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *Am J Clin Nutr* **70:**1040–1045.

Dulloo AG, Seydoux J, Girardier L, Chantre P, and Vandermander J (2000) Green tea and thermogenesis: interactions between catechin-polyphenols, caffeine and sympathetic activity. *Int J Obes Relat Metab Disord* **24:**252–258.

Dunk C, Enunwa M, De La Monte S, and Palmer R (2002) Increased fecal fat excretion in normal volunteers treated with lipase inhibitor ATL-962. *Int J Obes Relat Metab Disord* **26(Suppl):**S135.

Dwyer JT, Allison DB, and Coates PM (2005) Dietary supplements in weight reduction. *J Am Diet Assoc* **105(Suppl 1):** S80–S86.

Edwards CM, Stanley SA, Davis R, Brynes AE, Frost GS, Seal LJ, Ghatei MA, and Bloom SR (2001) Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol* **281:**E155–E1561.

Erondu N, Gantz I, Musser B, Suryawanshi S, Mallick M, Addy C, Cote GJ, Bray G, Fujioka K, Bays H, et al. (2006) Neuropeptide Y5 receptor antagonism does not induce clinically meaningful weight loss in overweight and obese adults. *Cell Metab* **4:**275–282.

Ettinger MP, Littlejohn TW, Schwartz SL, Weiss SR, McIlwain HH, Heymsfield SB, Bray GA, Roberts WG, Heyman ER, Stambler N, et al. (2003) Recombinant variant of ciliary neurotrophic factor for weight loss in obese adults: a randomized, dose-ranging study. *J Am Med Assoc* **289:**1826–1832.

Farooqi IS, Matarese G, Lord GM, Keogh JM, Lawrence E, Agwu C, Sanna V, Jebb SA, Perna F, Fontana S, et al. (2002) Beneficial effects of leptin on obesity T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Investig* **110:**1093–1103.

Fineman MS, Shen LZ, Taylor K, Kim DD, and Baron AD (2004) Effectiveness of progressive dose-escalation of exenatide (exendin-4) in reducing dose-limiting side effects in subjects with type 2 diabetes. *Diabetes Metab Res Rev* **20:**411–417.

Finer N, Bloom SR, Frost GS, Banks LM, and Griffiths J (2000) Sibutramine is effective for weight loss and diabetic control in obesity with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab* **2:**105–112.

Foltin RW, Haney M, Comer SD, and Fischman MW (1996) Effect of fenfluramine on food intake, mood, and performance of humans living in a residential laboratory. *Physiol Behav* **59:**295–305.

Fontbonne A, Charles MA, Juhan-Vague I, Bard JM, Andre P, Isnard F, Cohen JM, Grandmottet P, Vague P, Safar ME, et al. (1996) The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution: BIGPRO Study Group. *Diabetes Care* **19:**920–926.

Foxx-Orenstein A, Camilleri M, Stephens D, and Burton D (2003) Effect of a somatostatin analog on gastric motor and sensory functions in healthy humans. *Gut* **52:**1555–1561.

Franco C, Brandberg J, Lonn L, Andersson B, Bengtsson BA, and Johannsson G (2005) Growth hormone treatment reduces abdominal visceral fat in postmenopausal women with abdominal obesity: a 12-month placebo-controlled trial. *J Clin Endocrinol Metab* **90:**1466–1474.

Fujioka K, Seaton TB, Rowe E, Jelinek CA, Raskin P, Lebovitz HE, and Weinstein SP (2000) Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus. *Diabetes Obes Metab* **2:**175–187.

Gadde KM, Franciscy DM, Wagner HR 2nd, and Krishnan KR (2003) Zonisamide for weight loss in obese adults: a randomized controlled trial. *J Am Med Assoc* **289:**1820–1825.

Gadde KM, Parker CB, Maner LG, Wagner HR 2nd, Logue EJ, Drezner MK, and Krishnan KR (2001) Bupropion for weight loss: an investigation of efficacy and tolerability in overweight and obese women. *Obes Res* **9:**544–551.

Gadde KM, Yonish GM, Foust MS, Tam PY, and Najarian T (2006) A 24-week randomized controlled trial of VI-0521, a combination weight loss therapy, in obese adults. *Obesity* **14(Suppl):**A17–A18.

Gadde KM, Yonish GM, Wagner HR 2nd, Foust MS, and Allison DB (2006) Atomoxetine for weight reduction in obese women: a preliminary randomized controlled trial. *Int J Obes (Lond)* **30:**1138–1142.

Gedulin BR, Nikoulina SE, Smith PA, Gedulin G, Nielsen LL, Baron AD, Parkes DG, and Young AA (2005) Exenatide (exendin-4) improves insulin sensitivity and β-cell mass in insulin-resistant obese *fa/fa* Zucker rats independent of glycemia and body weight. *Endocrinology* **146:**2069–2076.

Gibson WT, Ebersole BJ, Bhattacharyya S, Clayton P, Farooqi IS, Sealfon SC, and O'Rahilly S (2004) Mutational analysis of the serotonin receptor 5HT2c in severe early-onset human obesity. *Can J Physiol Pharmacol* **82:**426–429.

Godoy-Matos A, Carraro L, Vieira A, Oliveira J, Guedes EP, Mattos L, Rangel C, Moreira RO, Coutinho W, and Appolinario JC (2005) Treatment of obese adolescents with sibutramine: a randomized, double-blind, controlled study. *J Clin Endocrinol Metab* **90:**1460–1465.

Goedecke JH, Barsdorf M, Beglinger C, Levitt NS, and Lambert EV (2003) Effects of a lipase inhibitor (Orlistat) on cholecystokinin and appetite in response to a high-fat meal. *Int J Obes Relat Metab Disord* **27:**1479–1485.

Gokcel A, Gumurdulu Y, Karakose H, Melek Ertorer E, Tanaci N, BascilTutuncu N, and Guvener N (2002) Evaluation of the safety and efficacy of sibutramine, orlistat and metformin in the treatment of obesity. *Diabetes Obes Metab* **4:**49–55.

Goldstein DJ, Rampey AH Jr, Roback PJ, Wilson MG, Hamilton SH, Sayler ME, and Tollefson GD (1995) Efficacy and safety of long-term fluoxetine treatment of obesity–maximizing success. *Obes Res* **3(Suppl 4):**481S–490S.

Greenway FL (1992) Clinical studies with phenylpropanolamine: a meta-analysis. *Am J Clin Nutr* **55(Suppl):**203S–205S.

Greenway FL (2001) The safety and efficacy of pharmaceutical and herbal caffeine and ephedrine use as a weight loss agent. *Obes Rev* **2:**199–211.

Greenway FL, Anderson JW, Atkinson RL, Fujioka K, Gadde KM, Gupta AK, O'Neil PM, Schumacher D, Smith DK, Whitehouse MJ, et al. (2006a) Bupropion and naltrexone for the treatment of obesity. *Diabetes Metab* **55(Suppl 1):**A394.

Greenway FL, Anderson JW, Atkinson RL, Fujioka K, Gadde KM, Gupta AK, O'Neil PM, Schumacher D, Smith DK, Whitehouse MJ, et al. (2006b) Bupropion and zonisamide for the treatment of obesity. *Obes Res* **14(Suppl):**A17.

Greenway FL, De Jonge L, Martin CK, Roberts AT, Grundy I, and Parker CB (2006c) Dietary herbal supplements with phenylephrine for weight loss. *J Med Food* **9:**572–578.

Greenway SE, Greenway FL 3rd, and Klein S (2002) Effects of obesity surgery on noninsulin-dependent diabetes mellitus. *Arch Surg* **137:**1109–1117.

Hackman RM, Havel PJ, Schwartz HJ, Rutledge JC, Watnik MR, Noceti EM, Stohs SJ, Stern JS, and Keen CL (2006) Multinutrient supplement containing ephedra and caffeine causes weight loss and improves metabolic risk factors in obese women: a randomized controlled trial. *Int J Obes (Lond)* **30:**1545–1556.

Haddock CK, Poston WS, Dill PL, Foreyt JP, and Ericsson M (2002) Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. *Int J Obes Relat Metab Disord* **26:**262–273.

Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, and Friedman JM (1995) Weight-reducing effects of the plasma protein encoded by the obese gene. *Science (Wash DC)* **269:**543–546.

Handlon A and Zhou H (2006) Melanin-concentrating hormone-1 receptor antagonists. *J Med Chem* **49:**4017–4022.

Hansen DL, Toubro S, Stock MJ, Macdonald IA, and Astrup A (1998) Thermogenic effects of sibutramine in humans. *Am J Clin Nutr* **68:**1180–1186.

Hauner H, Meier M, Wendland G, Kursheid T, and Lauterback KW (2000) Weight reduction by sibutramine in obese subjects in primary care medicine: the S.A.T. study (Abstract). *Int J Obes Metab Disord* **24:**S100.

Hauptman J (2000) Orlistat: selective inhibition of caloric absorption can affect long-term body weight. *Endocrine* **13:**201–206.

Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, and Brodows RG (2005) Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* **143:**559–569.

Heymsfield SB, Allison DB, Vasselli JR, Pietrobelli A, Greenfield D, and Nunez C (1998) *Garcinia cambogia* (hydroxycitric acid) as a potential antiobesity agent: a randomized controlled trial. *J Am Med Assoc* **280:**1596–1600.

Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, Lubina JA, Patane J, Self B, Hunt P, et al. (1999) Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *J Am Med Assoc* **282:**1568–1575.

Heymsfield SB, Segal KR, Hauptman J, Lucas CP, Boldrin MN, Rissanen A, Wilding JP, and Sjostrom L (2000) Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med* **160:**1321–1326.

Hill JO, Hauptman J, Anderson JW, Fujioka K, O'Neil PM, Smith DK, Zavoral JH, and Aronne LJ (1999) Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: a 1-y study. *Am J Clin Nutr* **69:**1108–1116.

Hoffman AR, Kuntze JE, Baptista J, Baum HB, Baumann GP, Biller BM, Clark RV, Cook D, Inzucchi SE, Kleinberg D, et al. (2004) Growth hormone (GH) replacement therapy in adult-onset GH deficiency: effects on body composition in men and women in a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab* **89:**2048–2056.

Hollander PA, Elbein SC, Hirsch IB, Kelley D, McGill J, Taylor T, Weiss SR, Crockett SE, Kaplan RA, Comstock J, et al. (1998) Role of orlistat in the treatment of obese patients with type 2 diabetes: a 1-year randomized double-blind study. *Diabetes Care* **21:**1288–1294.

Howarth NC, Saltzman E, and Roberts SB (2001) Dietary fiber and weight regulation. *Nutr Rev* **59:**129–139.

Hukshorn CJ, Westerterp-Plantenga MS, and Saris WH (2003) Pegylated human recombinant leptin (PEG-OB) causes additional weight loss in severely energy-restricted, overweight men. *Am J Clin Nutr* **77:**771–776.

Jackson HC, Needham AM, Hutchins LJ, Mazurkiewicz SE, and Heal DJ (1997) Comparison of the effects of sibutramine and other monoamine reuptake inhibitors on food intake in the rat. *Br J Pharmacol* **121:**1758–1762.

Jain AK, Kaplan RA, Gadde KM, Wadden TA, Allison DB, Brewer ER, Leadbetter RA, Richard N, Haight B, Jamerson BD, et al. (2002) Bupropion SR versus placebo for weight loss in obese patients with depressive symptoms. *Obes Res* **10:**1049–1056.

James WP, Astrup A, Finer N, Hilsted J, Kopelman P, Rossner S, Saris WH, and Van Gaal LF (2000) Effect of sibutramine on weight maintenance after weight loss: a randomized trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet* **356:**2119–2125.

Jordan J, Scholze J, Matiba B, Wirth A, Hauner H, and Sharma AM (2005) Influence of Sibutramine on blood pressure: evidence from placebo-controlled trials. *Int J Obes (Lond)* **29:**509–516.

Juan-Pico P, Fuentes E, Javier Bermudez-Silva F, Javier Diaz-Molina F, Ripoll C, Rodriguez de Fonseca F, and Nadal A (2006) Cannabinoid receptors regulate Ca^{2+} signals and insulin secretion in pancreatic β-cell. *Cell Calcium* **39:**155–162.

Kamath V, Jones CN, Yip JC, Varasteh BB, Cincotta AH, Reaven GM, and Chen YD (1997) Effects of a quick-release form of bromocriptine (Ergoset) on fasting and postprandial plasma glucose, insulin, lipid, and lipoprotein concentrations in obese nondiabetic hyperinsulinemic women. *Diabetes Care* **20:**1697–1701.

Kanatani A, Hata M, Mashiko S, Ishihara A, Okamoto O, Haga Y, Ohe T, Kanno T, Murai N, Ishii Y, et al. (2001) A typical Y1 receptor regulates feeding behaviors: effects of a potent and selective Y1 antagonist J-115814. *Mol Pharmacol* **59:**501–505.

Kastin AJ and Akerstrom V (2003) Entry of exendin-4 into brain is rapid but may be limited at high doses. *Int J Obes Relat Metab Disord* **27:**313–318.
Kaya A, Aydin N, Topsever P, Filiz M, Ozturk A, Dagar A, Kilinc E, and Ekmekcioglu C (2004) Efficacy of sibutramine, orlistat and combination therapy on short-term weight management in obese patients. *Biomed Pharmacother* **58:**582–587.
Kelley DE, Bray GA, Pi-Sunyer FX, Klein S, Hill J, Miles J, and Hollander P (2002) Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care* **25:** 1033–1041.
Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, and Baron AD (2005) Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* **28:**1083–1091.
Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, Morgenstern LB, Wilterdink JL, and Horwitz RI (2000) Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med* **343:**1826–1832.
Kim SH, Lee YM, Jee SH, and Nam CM (2003) Effect of sibutramine on weight loss and blood pressure: a meta-analysis of controlled trials. *Obes Res* **11:**1116–1123.
Kirkham TC (2005) Endocannabinoids in the regulation of appetite and body weight. *Behav Pharmacol* **16:**297–313.
Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, and Nathan DM (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* **346:**393–403.
Kopelman P, DeGroot G, Rissanen A, Rossner S, Toubro S, Bryson A, and Hallam R (2006) A randomized, placebo-controlled, trial of cetilistat (ATL-962), a novel lipase inhibitor and orlistat (Xenical) for the management of obese type 2 diabetic patients. *Diabetes Metab* **55(Suppl 1):**A395.
Kovacs EM, Lejeune MP, Nijs I, and Westerterp-Plantenga MS (2004) Effects of green tea on weight maintenance after body-weight loss. *Br J Nutr* **91:**431–437.
Kowalski TJ, Farley C, Cohen-Williams ME, Varty G, and Spar BD (2004) Melanin-concentrating hormone-1 receptor antagonism decreases feeding by reducing meal size. *Eur J Pharmacol* **497:**41–47.
Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, Jayathilake K, Meltzer HY, and Roth BL (2003) H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology* **28:**519–526.
Kromhout D, Bloemberg B, Seidell JC, Nissinen A, and Menotti A (2001) Physical activity and dietary fiber determine population body fat levels: the Seven Countries Study. *Int J Obes Relat Metab Disord* **25:**301–306.
Laferrere B, Abraham C, Russell CD, and Bowers CY (2005) Growth hormone releasing peptide-2 (GHRP-2), like ghrelin, increases food intake in healthy men. *J Clin Endocrinol Metab* **90:**611–614.
Larsen TM, Toubro S, and Astrup A (2003) Efficacy and safety of dietary supplements containing CLA for the treatment of obesity: evidence from animal and human studies. *J Lipid Res* **44:**2234–2241.
Larsen TM, Toubro S, van Baak MA, Gottesdiener KM, Larson P, Saris WH, and Astrup A (2002) Effect of a 28-d treatment with L-796568, a novel β_3-adrenergic receptor agonist, on energy expenditure and body composition in obese men. *Am J Clin Nutr* **76:**780–788.
Lawton CL, Wales JK, Hill AJ, and Blundell JE (1995) Serotoninergic manipulation, meal-induced satiety and eating pattern: effect of fluoxetine in obese female subjects. *Obes Res* **3:**345–356.
Leurs R, Bakker RA, Timmerman H, and de Esch IJ (2005) The histamine H3 receptor: from gene cloning to H3 receptor drugs. *Nat Rev Drug Discov* **4:**107–120.
Levens NR and Della-Zuana O (2003) Neuropeptide Y Y5 receptor antagonists as anti-obesity drugs. *Curr Opin Investig Drugs* **4:**1198–1204.
Levin BE and Dunn-Meynell AA (2000) Sibutramine alters the central mechanisms regulating the defended body weight in diet-induced obese rats. *Am J Physiol* **279:**R2222–R2228.
Li Z, Maglione M, Tu W, Mojica W, Arterburn D, Shugarman LR, Hilton L, Suttorp M, Solomon V, Shekelle PG, et al. (2005) Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med* **142:**532–546.
Lindgarde F (2000) The effect of orlistat on body weight and coronary heart disease risk profile in obese patients: the Swedish Multimorbidity Study. *J Intern Med* **248:**245–254.
Ludwig DS, Mountjoy KG, Tatro JB, Gillette JA, Frederich RC, Flier JS, and Maratos-Flier E (1998) Melanin-concentrating hormone: a functional melanocortin antagonist in the hypothalamus. *Am J Physiol* **274(Pt 1):** E627–E633.
Lugari R, Dei Cas A, Ugolotti D, Barilli AL, Camellini C, Ganzerla GC, Luciani A, Salerni B, Mittenperger F, Nodari S, et al. (2004) Glucagon-like peptide 1 (GLP-1) secretion and plasma dipeptidyl peptidase IV (DPP-IV) activity in morbidly obese patients undergoing biliopancreatic diversion. *Horm Metab Res* **36:**111–115.
Lustig RH, Greenway F, Velasquez-Mieyer P, Heimburger D, Schumacher D, Smith D, Smith W, Soler N, Warsi G, Berg W, et al. (2006) A multicenter, randomized, double-blind, placebo-controlled, dose-finding trial of a long-acting formulation of octreotide in promoting weight loss in obese adults with insulin hypersecretion. *Int J Obes (Lond)* **30:**331–341.
Lustig RH, Hinds PS, Ringwald-Smith K, Christensen RK, Kaste SC, Schreiber RE, Rai SN, Lensing SY, Wu S, and Xiong X (2003) Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* **88:**2586–2592.
Lustig RH, Rose SR, Burghen GA, Velasquez-Mieyer P, Broome DC, Smith K, Li H, Hudson MM, Heideman RL, and Kun LE (1999) Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. *J Pediatr* **135(Pt 1):**162–168.
Maahs D, de Serna DG, Kolotkin RL, Ralston S, Sandate J, Qualls C, and Schade DS (2006) Randomized, double-blind, placebo-controlled trial of orlistat for weight loss in adolescents. *Endocr Pract* **12:**18–28.
MacLean DB and Luo LG (2004) Increased ATP content/production in the hypothalamus may be a signal for energy-sensing of satiety: studies of the anorectic mechanism of a plant steroidal glycoside. *Brain Res* **1020:**1–11.
Maffei M, Fei H, Lee GH, Dani C, Leroy P, Zhang Y, Proenca R, Negrel R, Ailhaud G, and Friedman JM (1995) Increased expression in adipocytes of ob RNA in mice with lesions of the hypothalamus and with mutations at the *db* locus. *Proc Natl Acad Sci USA* **92:**6957–6960.
Maggs D, Shen L, Strobel S, Brown D, Kolterman O, and Weyer C (2003) Effect of pramlintide on A_{1c} and body weight in insulin-treated African Americans and Hispanics with type 2 diabetes: a pooled post hoc analysis. *Metabolism* **52:**1638–1642.
Mathus-Vliegen EM (2005) Long-term maintenance of weight loss with sibutramine in a GP setting following a specialist guided very-low-calorie diet: a double-blind, placebo-controlled, parallel group study. *Eur J Clin Nutr* **59(Suppl 1)**S31–S38; discussion S39.
McCarron DA, Morris CD, Henry HJ, and Stanton JL (1984) Blood pressure and nutrient intake in the United States. *Science (Wash DC)* **224:**1392–1398.
McElroy SL, Arnold LM, Shapira NA, Keck PE Jr, Rosenthal NR, Karim MR, Kamin M, and Hudson JI (2003) Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. *Am J Psychiatry* **160:**255–261.
McElroy SL, Kotwal R, Hudson JI, Nelson EB, and Keck PE (2004a) Zonisamide in the treatment of binge-eating disorder: an open-label, prospective trial. *J Clin Psychiatry* **65:**50–56.
McElroy SL, Shapira NA, Arnold LM, Keck PE, Rosenthal NR, Wu SC, Capece JA, Fazzio L, and Hudson JI (2004b) Topiramate in the long-term treatment of binge-eating disorder associated with obesity. *J Clin Psychiatry* **65:**1463–1469.
McMahon FG, Fujioka K, Singh BN, Mendel CM, Rowe E, Rolston K, Johnson F, and Mooradian AD (2000) Efficacy and safety of sibutramine in obese white and African American patients with hypertension: a 1-year, double-blind, placebo-controlled, multicenter trial. *Arch Intern Med* **160:**2185–2191.
McNulty SJ, Ur E, and Williams G (2003) A randomized trial of sibutramine in the management of obese type 2 diabetic patients treated with metformin. *Diabetes Care* **26:**125–131.
Meier AH, Cincotta AH, and Lovell WC (1992) Timed bromocriptine administration reduces body fat stores in obese subjects and hyperglycemia in type II diabetics. *Experientia (Basel)* **48:**248–253.
Merideth CH (2006) A single-center, double-blind, placebo-controlled evaluation of lamotrigine in the treatment of obesity in adults. *J Clin Psychiatry* **67:**258–262.
Mhurchu CN, Dunshea-Mooij C, Bennett D, and Rodgers A (2005) Effect of chitosan on weight loss in overweight and obese individuals: a systematic review of randomized controlled trials. *Obes Rev* **6:**35–42.
Miles JM, Leiter L, Hollander P, Wadden T, Anderson JW, Doyle M, Foreyt J, Aronne L, and Klein S (2002) Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. *Diabetes Care* **25:**1123–1128.
Mittendorfer B, Ostlund RE Jr, Patterson BW, and Klein S (2001) Orlistat inhibits dietary cholesterol absorption. *Obes Res* **9:**599–604.
Munro J, MacCuish A, Wilson E, and Duncan L (1968) Comparison of continuous and intermittent anorectic therapy in obesity. *Br Med J* **1:**352–354.
Nam SY, Kim KR, Cha BS, Song YD, Lim SK, Lee HC, and Huh KB (2001) Low-dose growth hormone treatment combined with diet restriction decreases insulin resistance by reducing visceral fat and increasing muscle mass in obese type 2 diabetic patients. *Int J Obes Relat Metab Disord* **25:**1101–1107.
Nann-Vernotica E, Donny EC, Bigelow GE, and Walsh SL (2001) Repeated administration of the D1/5 antagonist ecopipam fails to attenuate the subjective effects of cocaine. *Psychopharmacology* **155:**338–347.
Nasir JM, Durning SJ, Ferguson M, Barold HS, and Haigney MC (2004) Exercise-induced syncope associated with QT prolongation and ephedra-free Xenadrine. *Mayo Clin Proc* **79:**1059–1062.
National Heart, Lung, and Blood Institute and North American Association for the Study of Obesity (2000) *The Practical Guide: Identification, Evaluation and Treatment of Overweight and Obesity in Adults*, National Institutes of Health, Bethesda, MD.
National Institutes of Health Consensus Development Conference Statement (1985) Health implications of obesity. *Ann Intern Med* **103:**977–1077.
Nilsson B (2006) 5-Hydroxytryptamine 2C (5-HT2C) receptor agonists as potential antiobesity agents. *J Med Chem* **49:**4023–4034.
Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Kim C, and Lau J (2004) Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med* **164:**1395–1404.
Nykamp DL, Fackih MN, and Compton AL (2004) Possible association of acute lateral-wall myocardial infarction and bitter orange supplement. *Ann Pharmacother* **38:**812–816.
O'Donovan D, Feinle-Bisset C, Wishart J, and Horowitz M (2003) Lipase inhibition attenuates the acute inhibitory effects of oral fat on food intake in healthy subjects. *Br J Nutr* **90:**849–852.
Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, Wagner AJ, DePaoli AM, Reitman ML, Taylor SI, et al. (2002) Leptin-replacement therapy for lipodystrophy. *N Engl J Med* **346:**570–578.
Ortega-Gonzalez C, Luna S, Hernandez L, Crespo G, Aguayo P, Arteaga-Troncoso G, and Parra A (2005) Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome. *J Clin Endocrinol Metab* **90:**1360–1365.
Padwal R, Li SK, and Lau DC (2004) Long-term pharmacotherapy for obesity and overweight. *Cochrane Database Syst Rev* CD004094.
Padwal R, Majumdar SR, Johnson JA, Varney J, and McAlister FA (2005) A systematic review of drug therapy to delay or prevent type 2 diabetes. *Diabetes Care* **28:**736–744.
Pagotto U, Marsicano G, Cota D, Lutz B, and Pasquali R (2006) The emerging role of the endocannabinoid system in endocrine regulation and energy balance. *Endocr Rev* **27:**73–100.
Paranjpe P, Patki P, and Patwardhan B (1990) Ayurvedic treatment of obesity: a randomized double-blind, placebo-controlled clinical trial. *J Ethnopharmacol* **29:** 1–11.

Parker E, Van Heek M, and Stamford A (2002) Neuropeptide Y receptors as targets for anti-obesity drug development: perspective and current status. *Eur J Pharmacol* **440:**173–187.

Pathy J, Menon G, Reynolds A, and Van Strik R (1977) Betahistine hydrochloride (Serc) in cerebrovascular disease: a placebo-controlled study. *Age Ageing* **6:**179–184.

Patriti A, Facchiano E, Sanna A, Gulla N, and Donini A (2004) The enteroinsular axis and the recovery from type 2 diabetes after bariatric surgery. *Obes Surg* **14:**840–848.

Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, and Rosenstock J (2006) 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. *J Am Med Assoc* **295:**761–775.

Pi-Sunyer X, Kissileff HR, Thornton J, and Smith GP (1982) C-terminal octapeptide of cholecystokinin decreases food intake in obese men. *Physiol Behav* **29:**627–630.

Pijl H, Ohashi S, Matsuda M, Miyazaki Y, Mahankali A, Kumar V, Pipek R, Iozzo P, Lancaster JL, Cincotta AH, et al. (2000) Bromocriptine: a novel approach to the treatment of type 2 diabetes. *Diabetes Care* **23:**1154–1161.

Pittler MH and Ernst E (2004) Dietary supplements for body-weight reduction: a systematic review. *Am J Clin Nutr* **79:**529–536.

Pittler MH and Ernst E (2005) Complementary therapies for reducing body weight: a systematic review. *Int J Obes (Lond)* **29:**1030–1038.

Poindexter GS, Bruce MA, LeBoulluec KL, Monkovic I, Martin SW, Parker EM, Iben LG, McGovern RT, Ortiz AA, Stanley JA, et al. (2002) Dihydropyridine neuropeptide Y Y_1 receptor antagonists. *Bioorg Med Chem Lett* **12:**379–382.

Poston WS, Haddock CK, Dill PL, Thayer B, and Foreyt JP (2001) Lifestyle treatments in randomized clinical trials of pharmacotherapies for obesity. *Obes Res* **9:**552–563.

Poyurovsky M, Tal V, Maayan R, Gil-Ad I, Fuchs C, and Weizman A (2004) The effect of famotidine addition on olanzapine-induced weight gain in first-episode schizophrenia patients: a double-blind placebo-controlled pilot study. *Eur Neuropsychopharmacol* **14:**332–336.

Puhl RM and Brownell KD (2003) Psychosocial origins of obesity stigma: toward changing a powerful and pervasive bias. *Obes Rev* **4:**213–227.

Putnam J (1893) Cases of myxedema and acromegalia treated with benefit by sheep's thyroids: recent observations respecting the pathology of the cachexias following disease of the thyroid; clinical relationships of grave's disease and acromegalia. *Am J Med Sci* **106:**125–148.

Ratner RE, Dickey R, Fineman M, Maggs DG, Shen L, Strobel SA, Weyer C, and Kolterman OG (2004) Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabete Med* **21:**1204–1212.

Ratner RE, Maggs D, Nielsen LL, Stonehouse AH, Poon T, Zhang B, Bicsak TA, Brodows RG, and Kim DD (2006) Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. *Diabetes Obes Metab* **8:**419–428.

Reaven G, Segal K, Hauptman J, Boldrin M, and Lucas C (2001) Effect of orlistat-assisted weight loss in decreasing coronary heart disease risk in patients with syndrome X. *Am J Cardiol* **87:**827–831.

Redmon JB, Reck KP, Raatz SK, Swanson JE, Kwong CA, Ji H, Thomas W, and Bantle JP (2005) Two-year outcome of a combination of weight loss therapies for type 2 diabetes. *Diabetes Care* **28:**1311–1315.

Riddle MC and Drucker DJ (2006) Emerging therapies mimicking the effects of amylin and glucagon-like peptide 1. *Diabetes Care* **29:**435–449.

Riserus U, Smedman A, Basu S, and Vessby B (2004) Metabolic effects of conjugated linoleic acid in humans: the Swedish experience. *Am J Clin Nutr* **79:**1146S–1148S.

Rodriquez de Fonseca F, Navarro M, Alvarez E, Roncero I, Chowen JA, Maestre O, Gomez R, Munoz RM, Eng J, and Blazquez E (2000) Peripheral versus central effects of glucagon-like peptide-1 receptor agonists on satiety and body weight loss in Zucker obese rats. *Metabolism* **49:**709–717.

Rogers PJ and Blundell JE (1979) Effect of anorexic drugs on food intake and the micro-structure of eating in human subjects. *Psychopharmacology* **66:**159–165.

Rolls BJ, Shide DJ, Thorwart ML, and Ulbrecht JS (1998) Sibutramine reduces food intake in nondieting women with obesity. *Obes Res* **6:**1–11.

Rosenbaum M, Murphy EM, Heymsfield SB, Matthews DE, and Leibel RL (2002) Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. *J Clin Endocrinol Metab* **87:**2391–2394.

Rossi R, Del Prete E, and Scharrer E (1999) Effect of the H1-histamine receptor agonist betahistine on drinking and eating behavior in pygmy goats. *Physiol Behav* **66:**517–521.

Rossner S, Sjostrom L, Noack R, Meinders AE, and Noseda G (2000) Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity: European Orlistat Obesity Study Group. *Obes Res* **8:**49–61.

Roth D, Weyer C, Anderson CE, Parkes DG, and Baron AD (2006) Leptin responsivity restored in leptin-resistant diet-induced obese rats: synergistic actions of amylin and leptin for reduction in body weight and fat. Handout from *American Diabetes Association 66th Annual Scientific Sessions*; 2006 June 9–13; Washington, DC.

Rupnick MA, Panigrahy D, Zhang CY, Dallabrida SM, Lowell BB, Langer R, and Folkman MJ (2002) Adipose tissue mass can be regulated through the vasculature. *Proc Natl Acad Sci USA* **99:**10730–10735.

Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, and Willett WC (1997) Dietary fiber, glycemic load, and risk of noninsulin-dependent diabetes mellitus in women. *J Am Med Assoc* **277:**472–477.

Sari R, Balci MK, Cakir M, Altunbas H, and Karayalcin U (2004) Comparison of efficacy of sibutramine or orlistat versus their combination in obese women. *Endocr Res* **30:**159–167.

Scheen AJ, Finer N, Hollander P, Jensen MD, and Van Gaal LF (2006) Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomized controlled study. *Lancet* **368:**1660–1672.

Schteingart DE (1992) Effectiveness of phenylpropanolamine in the management of moderate obesity. *Int J Obes Relat Metab Disord* **16:**487–493.

Seagle HM, Bessesen DH, and Hill JO (1998) Effects of sibutramine on resting metabolic rate and weight loss in overweight women. *Obes Res* **6:**115–121.

Seipel JH, Fisher R, Blatchley RJ, Floam J, and Bohm M (1977) Rheoencephalographic and other studies of betahistine in humans. IV. Prolonged administration with improvement in arteriosclerotic dementia. *J Clin Pharmacol* **17:**140–161.

Shapira NA, Goldsmith TD, and McElroy SL (2000) Treatment of binge-eating disorder with topiramate: a clinical case series. *J Clin Psychiatry* **61:**368–372.

Shapira NA, Lessig MC, Lewis MH, Goodman WK, and Driscoll DJ (2004) Effects of topiramate in adults with Prader-Willi syndrome. *Am J Ment Retard* **109:**301–309.

Shapira NA, Lessig MC, Murphy TK, Driscoll DJ, and Goodman WK (2002) Topiramate attenuates self-injurious behavior in Prader-Willi syndrome. *Int J Neuropsychopharmacol* **5:**141–145.

Shapses SA, Heshka S, and Heymsfield SB (2004) Effect of calcium supplementation on weight and fat loss in women. *J Clin Endocrinol Metab* **89:**632–637.

Shapses SA, Von Thun NL, Heymsfield SB, Ricci TA, Ospina M, Pierson RN Jr, and Stahl T (2001) Bone turnover and density in obese premenopausal women during moderate weight loss and calcium supplementation. *J Bone Miner Res* **16:**1329–1336.

Shearman LP, Camacho RE, Sloan Stribling D, Zhou D, Bednarek MA, Hreniuk DL, Feighner SD, Tan CP, Howard AD, Van der Ploeg LH, et al. (2003) Chronic MCH-1 receptor modulation alters appetite, body weight and adiposity in rats. *Eur J Pharmacol* **475:**37–47.

Shekelle PG, Hardy ML, Morton SC, Maglione M, Mojica WA, Suttorp MJ, Rhodes SL, Jungvig L, and Gagne J (2003) Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. *J Am Med Assoc* **289:**1537–1545.

Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjostrom CD, et al. (2004) Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* **351:**2683–2693.

Sjostrom L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, and Krempf M (1998) Randomized placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients: European Multicenter Orlistat Study Group. *Lancet* **352:**167–172.

Small CJ and Bloom SR (2004) Gut hormones as peripheral anti obesity targets. *Curr Drug Targets CNS Neurol Disord* **3:**379–388.

Smathers SA, Wilson JG, and Nigro MA (2003) Topiramate effectiveness in Prader-Willi syndrome. *Pediatr Neurol* **28:**130–133.

Smith IG and Goulder MA (2001) On behalf of the members of the sibutramine clinical study 1047 team. Randomized placebo-controlled trial of long-term treatment with sibutramine in mild to moderate obesity. *J Fam Pract* **50:**505–512.

Smith SR, Prosser W, Donahue D, Anderson CE, and Shanahan W (2006) APD356, an orally-active selective 5HT2c agonist reduces body weight in obese men and women. *Diabetes Metab* **55(Suppl 1):**A80.

Snow V, Barry P, Fitterman N, Qaseem A, and Weiss K (2005) Pharmacologic and surgical management of obesity in primary care: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* **142:**525–531.

Souers AJ, Gao J, Brune M, Bush E, Wodka D, Vasudevan A, Judd AS, Mulhern M, Brodjian S, Dayton B, et al. (2005) Identification of 2-(4-benzyloxyphenyl)-*N*-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indazol-6-yl]acetamide, an orally efficacious melanin-concentrating hormone receptor 1 antagonist for the treatment of obesity. *J Med Chem* **48:**1318–1321.

Sullivan C and Triscari J (1977) Metabolic regulation as a control for lipid disorders. Influence of (−)-hydroxycitrate on experimentally induced obesity in the rodent. *Am J Clin Nutr* **30:**767–776.

Szayna M, Doyle ME, Betkey JA, Holloway HW, Spencer RG, Greig NH, and Egan JM (2000) Exendin-4 decelerates food intake, weight gain, and fat deposition in Zucker rats. *Endocrinology* **141:**1936–1941.

Szelag A, Trocha M, and Merwid-Lad A (2001) Betahistine inhibits food intake in rats. *Pol J Pharmacol* **53:**701–707.

Tan TM, Vanderpump M, Khoo B, Patterson M, Ghatei MA, and Goldstone AP (2004) Somatostatin infusion lowers plasma ghrelin without reducing appetite in adults with Prader-Willi syndrome. *J Clin Endocrinol Metab* **89:**4162–4165.

Tighilet B, Trottier S, Mourre C, Chotard C, and Lacour M (2002) Betahistine dihydrochloride interaction with the histaminergic system in the cat: neurochemical and molecular mechanisms. *Eur J Pharmacol* **446:**63–73.

Torgerson JS, Hauptman J, Boldrin MN, and Sjostrom L (2004) 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* **27:**155–161.

van Baak MA, Hul GB, Toubro S, Astrup A, Gottesdiener KM, DeSmet M, and Saris WH (2002) Acute effect of L-796568, a novel β_3-adrenergic receptor agonist, on energy expenditure in obese men. *Clin Pharmacol Ther* **71:**272–279.

Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, and Rossner S (2005) Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* **365:**1389–1397.

Velasquez-Mieyer PA, Cowan PA, Arheart KL, Buffington CK, Spencer KA, Connelly BE, Cowan GW, and Lustig RH (2003) Suppression of insulin secretion is associated with weight loss and altered macronutrient intake and preference in a subset of obese adults. *Int J Obes Relat Metab Disord* **27:**219–226.

Vettor R, Serra R, Fabris R, Pagano C, and Federspil G (2005) Effect of sibutramine on weight management and metabolic control in type 2 diabetes: a meta-analysis of clinical studies. *Diabetes Care* **28:**942–949.

Wadden TA, Berkowitz RI, Sarwer DB, Prus-Wisniewski R, and Steinberg C (2001) Benefits of lifestyle modification in the pharmacologic treatment of obesity: a randomized trial. *Arch Intern Med* **161:**218–227.

Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Arnold ME, and Steinberg CM (2000) Effects of sibutramine plus orlistat in obese women following 1 year of treatment by sibutramine alone: a placebo-controlled trial. *Obes Res* **8:**431–437.

Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Phelan S, Cato RK, Hesson LA, Osei SY, Kaplan R, and Stunkard AJ (2005) Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med* **353:**2111–2120.

Walsh AE, Smith KA, Oldman AD, Williams C, Goodall EM, and Cowen PJ (1994) m-Chlorophenylpiperazine decreases food intake in a test meal. *Psychopharmacology (Berl)* **116:**120–122.

Westerterp-Plantenga MS, Lejeune MP, and Kovacs EM (2005) Body weight loss and weight maintenance in relation to habitual caffeine intake and green tea supplementation. *Obes Res* **13:**1195–1204.

Wilding J, Van Gaal L, Rissanen A, Vercruysse F, and Fitchet M (2004) 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 Relat Metab Disord* **28:**1399–1410.

Winkelman JW (2003) Treatment of nocturnal eating syndrome and sleep-related eating disorder with topiramate. *Sleep Med* **4:**243–246.

Wirth A and Krause J (2001) Long-term weight loss with sibutramine: a randomized controlled trial. *J Am Med Assoc* **286:**1331–1339.

Wolk A, Manson JE, Stampfer MJ, Colditz GA, Hu FB, Speizer FE, Hennekens CH, and Willett WC (1999) Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. *J Am Med Assoc* **281:**1998–2004.

Wynne K, Park AJ, Small CJ, Patterson M, Ellis SM, Murphy KG, Wren AM, Frost GS, Meeran K, Ghatei MA, et al. (2005) Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial. *Diabetes* **54:**2390–2395.

Yanovski SZ and Yanovski JA (2002) Obesity. *N Engl J Med* **346:**591–602.

Zahorska-Markiewicz B, Obuchowicz E, Waluga M, Tkacz E, and Herman ZS (2001) Neuropeptide Y in obese women during treatment with adrenergic modulation drugs. *Med Sci Monit* **7:**403–408.

Zemel MB, Richards J, Mathis S, Milstead A, Gebhardt L, and Silva E (2005a) Dairy augmentation of total and central fat loss in obese subjects. *Int J Obes (Lond)* **29:**391–397.

Zemel MB, Richards J, Milstead A, and Campbell P (2005b) Effects of calcium and dairy on body composition and weight loss in African-American adults. *Obes Res* **13:**1218–1225.

Zemel MB, Shi H, Greer B, Dirienzo D, and Zemel PC (2000) Regulation of adiposity by dietary calcium. *FASEB J* **14:**1132–1138.

Zemel MB, Thompson W, Milstead A, Morris K, and Campbell P (2004) Calcium and dairy acceleration of weight and fat loss during energy restriction in obese adults. *Obes Res* **12:**582–590.

Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, and Friedman JM (1994) Positional cloning of the mouse obese gene and its human homolog. *Nature (Lond)* **372:**425–432.

Zhi J, Mulligan TE, and Hauptman JB (1999) Long-term systemic exposure of orlistat, a lipase inhibitor, and its metabolites in obese patients. *J Clin Pharmacol* **39:**41–46.