

# Current and Potential Drugs for Treatment of Obesity

GEORGE A. BRAY AND FRANK L. GREENWAY

*Louisiana State University, Pennington Biomedical Research Center, Baton Rouge, Louisiana  
70808-4124*

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## I. Introduction

WHEN 1997 began there was great optimism because, for the first time in 25 yr, a new drug for the treatment of obesity had been approved by the US Food and Drug Administration (FDA) in April 1996, and two more drugs were beginning their way through the approval process (1). As the year closed this optimism had been dashed by three events. The first was the report in July and publication in August of 24 women who had developed an unusual form of valvular heart disease while being treated with fenfluramine and phentermine (2). From the initial report, the number of patients with this problem grew until the only prudent move was to withdraw fenfluramine and dexfenfluramine from the market. This happened on September 15, 1997. The second event was the temporary withdrawal of the new drug application for orlistat, a drug that blocks intestinal lipase and produces weight loss. The third event was the delay in the marketing of sibutramine, which had received a letter of approval from the FDA and had originally been planned for marketing in late 1997.

This sequence of events provides the background for this review of treatment for obesity. In the aftermath of the events of 1997, one might conclude that we should not use drugs to treat obesity (3, 4). If people would only push themselves away from the table, there would be no problem of obesity. Another conclusion might be that we should wait until we have more information about the molecular and physiological basis for obesity before designing new medications to help the obese (5). We reject both of these conclusions (1).

The history of drug treatment for obesity is indeed strewn with catastrophes (6–8). This is shown in Table 1, which presents a historical tabulation of several treatments that have been tried during this century along with their unintended consequences. Thyroid extract was the first drug tried and was reportedly used as early as 1893 (9). To achieve the effects on body weight, the doses required produce some measure of hyperthyroidism with catabolic consequences on bone, muscle, and the heart. When dinitrophenol was first used in 1933 (6, 10) it was followed by neuropathy and cataracts, which led to its discontinuation. The introduction of amphetamine in 1937 (11, 12) was followed by reports of addiction, a problem that has plagued all of the chemicals that are structurally similar to amphetamine whether they are addictive or not. The use of pills containing amphetamine, digitalis, and diuretics led to several deaths in 1967 and prompted the US Senate to hold hearings. Sadly, as is often the case with such grandstanding, nothing concrete happened to prevent subsequent problems. In 1971 aminorex, or aminoxaphen, a new appetite suppressant, was taken off the market in Europe shortly after marketing because of an outbreak of pulmonary hypertension linked to this drug (13). A few years later in 1978, 17 deaths were reported with the use of very-low-calorie diets containing collagen as the principal source of protein (14). Problems with diet clinics led to another set of congressional hearings in 1991, again with little impact except the bankruptcy of several commercial weight loss programs. The final problem has been the valvular heart disease associated with the combined use of fenfluramine and phentermine (2).

All of this brings us back to the realities of obesity. Obesity is a chronic, stigmatized disease (6, 15). In this context, we define disease in the same sense that hypertension and hypercholesterolemia are defined as diseases (1, 16, 17). Each of them is a risk factor that is associated with increased risks of a defined set of endpoints. For hypertension, the endpoints are heart failure and stroke. For hypercholesterolemia, they are atherosclerosis and coronary artery disease. For an increase in body mass index, as a measure of obesity, it is the risk of diabetes mellitus, hypertension, dyslipidemia, certain forms of cancer, sleep apnea, and osteoarthritis. Professor Flemyng (18) grasped the essence of obesity as a disease more than 250 yr ago when he said:

“Corpulency, when in an extraordinary degree, may be reckoned a disease, as it in some measure obstructs the free exercise of the animal functions; and hath a tendency to shorten life, by paving the way to dangerous distempers.”

Data collected in the United States by the National Center

Address reprint requests to: George A. Bray, M.D., 6400 Perkins Road, Baton Rouge, Louisiana 70808 USA.

for Health Statistics show that the prevalence of obesity, defined as a body mass index >30 kg/m<sup>2</sup>, has steadily risen from 12.8% in 1976–1980 to 22.5% in 1988–1994 (19, 20). Using a body mass index (BMI) of >25 kg/m<sup>2</sup>, more than 50% of Americans, or 97 million adults, are overweight (21). In the United Kingdom, the percentage with a BMI >30 kg/m<sup>2</sup> has increased from 6% to 13% for men and from 8% to 16% for women between 1986 and 1993 (22). These data and data from other countries (23) are indicative of a major international epidemic of obesity.

With recognition of this epidemic of obesity has come an increasing awareness of the need to improve the quality and effectiveness of available treatments. Obesity is a chronic disease, for which none of the current medications provide a cure. Thus, when treatment is stopped patients regain body weight since the disease is still present (1, 16, 17). The current core of treatment for obesity includes behavior therapy aimed at modifying eating-related activities, exercise to increase caloric expenditure, and diets to lower calorie and fat intake. Pharmacological treatments are generally considered as an adjunct to this core therapy (24, 25).

TABLE 1. History of drug treatments for obesity

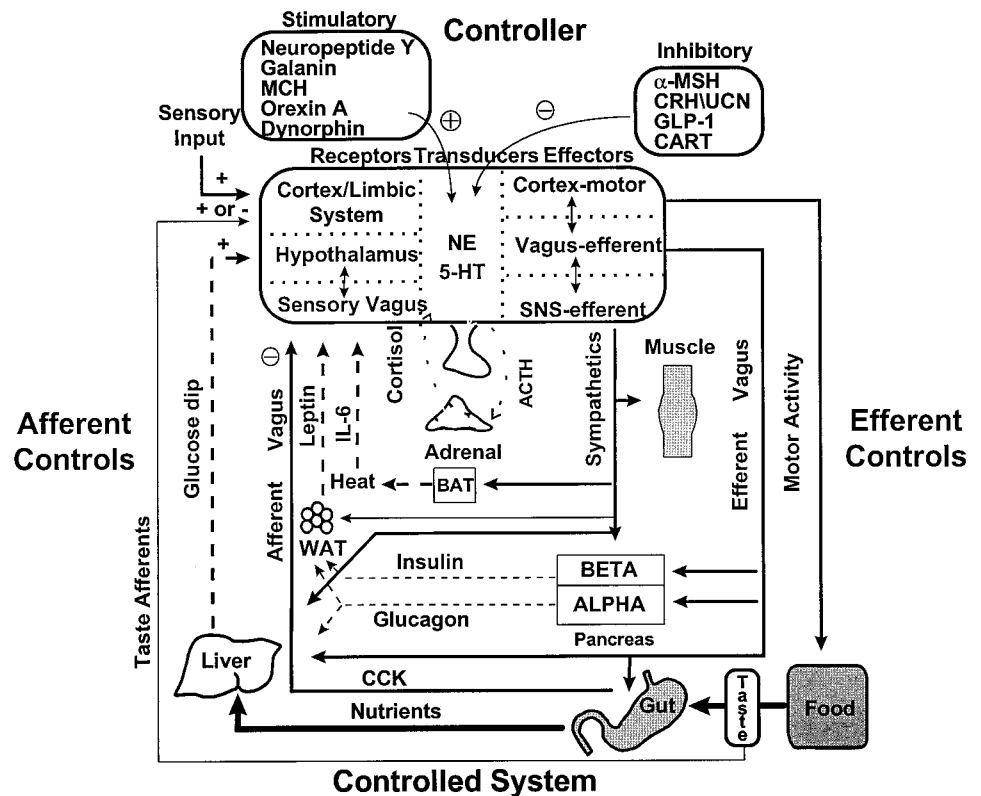
Date	Drug	Outcome
1893	Thyroid	Hyperthyroidism
1934	Dinitrophenol	Cataracts; neuropathy
1937	Amphetamine	Addiction
1967	Rainbow pills (digitalis; diuretics)	Deaths
1971	Aminorex	Pulmonary hypertension
1978	Collagen-based VLCD	Deaths
1997	Fenfluramine/phentermine	Valvular insufficiency

VLCD, Very-low calorie diet.

A few types of obesity, such as Cushing's Disease and insulinoma, are susceptible to cure by surgical intervention, but most other causes of obesity require chronic, long-term treatment. Since obesity can only rarely be cured, palliative treatment is indicated when the risks of obesity outweigh the risks of treatment.

From the time when, more than 20 yr ago, the post-World War II literature on experimental obesity was summarized (6, 12, 26, 27), the understanding of the basic physiological mechanisms that control food intake and body fat stores has expanded rapidly (28–32). It has provided increasing opportunities to develop new strategies for dealing with obesity using medications. This review examines the existing pharmacological approaches to treating obesity as well as some of the potential newer approaches that may yield rewarding drugs in the future. As a framework for this discussion, we will use a feedback model. Such a model contains a controlled system that ingests, digests, absorbs, metabolizes, stores, and excretes nutrients. The controlled system generates afferent signals that monitor the state of the controlled system and provide information to the controller in the brain that receives, transduces, and acts on this information, and efferent controls that direct food intake, hormonal responses, and energy expenditure. Figure 1 depicts many of the elements in this system. They will be reviewed in more detail below. The afferent signals from adipose tissue and signals transmitted through the vagus from the gut and elsewhere provide a satiety system that restrains or terminates eating. The central system receives these satiety signals and integrates them with information from the environment in reaching decisions about eating or alternative activities. A growing

FIG. 1. A feedback model for control and regulation on body fat stores (MCH, melanin-concentrating hormone; UCN, urocortin; GLP-1, glucagon-like peptide-1 (glucagon 6–29); CART, cocaine amphetamine-regulated transcript; NE, norepinephrine; and 5-HT, serotonin).



number of peptides act on basic monoamine and amino acid signals to modulate this process. Efferent signals that direct food seeking, ingestion, and the release of hormones modulating gastrointestinal (GI) function in response to food intake are controlled by the brain. Viewed from this feedback model, we can identify three broad mechanisms that we will use to classify treatments of obesity. The first is treatments that reduce energy intake. The second broad strategy is to shift metabolism from one nutrient to another and generate signals that will reduce food intake. The third approach is to increase energy expenditure, thereby using more calories and leaving less for storage.

Obesity and hypertension have a number of features in common that may guide the future of drug development (1, 16). Before the introduction of chlorothiazide in 1958, hypertension had three major treatments: diet, drugs, and surgery. A low-salt diet was the dietary mainstay. If begun early enough, a very-low-salt diet could be beneficial in treating hypertension. When effective pharmacological therapy began to appear from 1958 onward, the emphasis on very-low-salt diets waned. Drug treatment for hypertension before 1958 included reserpine, hydralazine, and ganglionic blockers. The side effects of these drugs were substantial and limited their use. Finally, surgical sympathectomy was a drastic method used effectively in some people. The analogy with treatment of obesity are the low- and very-low-calorie diets, the use of drugs which, regrettably, have significant side effects, and the use of gastric and intestinal bypass surgery.

In 1958 chlorothiazide was introduced. By producing a diuresis, sodium excretion was increased and the first effective treatment for hypertension appeared. Orlistat, a pancreatic lipase inhibitor, might be viewed as an analog of the diuretic. The loss of calories as undigested triglycerides would be like the loss of sodium with diuretics. The centrally active noradrenergic and serotonergic drugs approved by the FDA for treatment of obesity described in detail below may be analogous to the earlier drugs used to treat hypertension. Finally, sympathectomy for treating hypertension is analogous to gastric surgery for obesity.

If today's treatment for obesity is analogous to the treatment for hypertension in 1958, we can expect a variety of new and effective drugs. Some of these will act at the level of the controller to modulate feeding. Others will work at the level of the afferent signaling system to modulate feeding. Other drugs are likely to control obesity by modulating metabolic processes in the controlled system like the drugs for hypertension that affect the angiotensin system or nitric oxide. Finally, there will be drugs that modulate afferent signals.

This review focuses on current and potential treatments for obesity. These will be grouped within each of the three categories listed above: those that reduce food intake; those that shift nutrient metabolism; and those that increase energy expenditure. Within each of these categories, the mechanisms will be subdivided by whether they act peripherally or centrally. This division is in some instances arbitrary, but represents the authors' best judgment. As indicated in Fig. 1, sensory signals such as sight, sound, and early taste of food are usually positive signals, although a frightening environment or bad taste of food may be aversive and inhibit eating.

GI signals such as cholecystokinin, gastric or intestinal distention, or absorbed nutrients usually inhibit further eating. Leptin is one of the major inhibitory signals (see below). Within the brain or controller are the receivers and transducers that transform peripheral information, relating environmental messages to the strength or weakness of peripheral satiety signals. The output from these transducers can stimulate or inhibit the effector system for food seeking. It is in this context that this review has been organized. For those wishing additional information on obesity and specifically on drug treatment, a number of monographs and reviews have been published in the last 50 yr (6, 21, 23–25, 28–100). This list covers most if not all of them.

## II. Criteria for Evaluating the Efficacy of Antiobesity Treatment

This section deals with the criteria for evaluating the efficacy of treatment for obesity. The initial criteria proposed after World War II were to estimate the amount of weight loss either in absolute terms or relative to initial weight. In any comparison the weight loss should be compared with a placebo. Weight loss in placebo-treated groups is highly variable from one study to another and needs to be considered in the review of any drug-treatment protocol. Recently, the FDA in the United States and the Committee for Proprietary Medicinal Products (CPMP) in Europe have proposed more unified protocols. In this review we have used the FDA criterion of a weight loss of more than 5% below placebo and the CPMP criterion of a 10% weight loss below baseline to compare drug trials.

A number of criteria have been proposed for evaluating the response to treatment for obesity. In the present context, we will deal with the approaches used since 1945. For earlier reviews the readers are referred to other publications (6, 8, 101, 102). Table 2 lists several criteria for evaluating success in treating obesity. In a now classic paper by Stunkard and McLauren-Hume (103) the criterion for success was based on the percentage of people in drug-treated and control groups who lost more than 20 pounds (9 kg) or those who lost more than 40 pounds (18 kg). Asher and Dietz (42) used these criteria in their review of treatments for obesity in 1972. The problem with these criteria is that some individuals in any treatment program may not need to lose more than 20 pounds (9 kg) or more than 40 pounds (18 kg). In addition, the amount of weight loss is greater for men than women with any comparable degree of caloric restriction because women have less lean body mass for any given weight. Also, heavier subjects tend to lose more weight than lighter ones. Trulson *et al.* (104) proposed criteria that scaled the amount of weight loss to the subjects initial weight. Feinstein (105) took a similar approach and defined a "Reduction Index," which is similar to the loss of percentage of excess weight that is still widely used by surgeons in their evaluation of the results with various operative procedures for obesity. The reduction index has been used in a few studies (109–111).

In an early FDA review of drugs (106), two criteria were used to evaluate weight loss. The first was the rate of weight loss compared with placebo, which can be useful when the

TABLE 2. Some criteria for assessing success in treatment for obesity

Author	Criteria
Stunkard and McLauren-Hume (103)	Percent losing >20 lb (9 kg) Percent losing >40 lb (18.1 kg)
Trulson <i>et al.</i> (104)	Success: (initial wt in lb lost) ≤ 150 lb ≥ 10 lb, 151–175 lb ≥ 15 lb, 176–200 lb/20 lb, 201–225 lb/25 lb, 225–250 lb/30 lb, ≥251 lb/35 lb Failure: ≤5 lb wt loss in 4 or > months
Feinstein (105)	Reduction Index = wt (lost) $\left[ \frac{\text{Initial wt}}{(\text{Surplus wt}) \times (\text{Target wt})} \right] \times 100$
Scoville (106)	>0.5 lb/wk more than placebo
Atkinson (107)	Percent losing >1 lb/wk or >3 lb/wk ≥10% loss of excess weight for >6 mo loss of ≥2 BMI units for >6 mo Reduction in co-morbidities for >6 mo
Bray (108)	≥5% wt loss if BMI >27 kg/m <sup>2</sup> ≥20% loss of excess body weight >5% reduction in visceral fat significant improvements in comorbidities

lb, Pound; wk, week; mo, month; wt, weight.

studies are short term. The second criterion was a responder analysis asking what percent of subjects lost more than 1 pound/wk (0.45 kg/wk) or more than 3 pounds/wk (1.4 kg/wk).

Both the USFDA and the CPMP of the European Agency for the Evaluation of Medicinal Product (EMA) have proposed criteria to be met by drugs approved for the treatment of obesity (112, 113). These are summarized in Table 3. The FDA has suggested a weight loss of more than 5% greater than placebo that is significantly greater than placebo. The CPMP has suggested a 10% loss of weight from baseline that is significantly greater than placebo. A number of secondary criteria are also listed along with inclusion criteria and dose-ranging responses. Men and women should be included if they are otherwise healthy with a BMI above 30 kg/m<sup>2</sup> or above 27 kg/m<sup>2</sup> if comorbidities such as hypertension or diabetes are present. Both agencies propose a run-in. The CPMP encourages active placebo treatment and does not specify a difference from placebo, as long as the drug effect is significantly greater. Studies showing maintenance of weight loss are encouraged by both agencies. A decrease in BMI has also been proposed (110).

Categorical analysis of the percentage of patients who have achieved more than a 5% or 10% weight loss is similar to the responder analysis used in the initial drug evaluation by Scoville (106) and has also been proposed in the FDA Guidance (112) and the CPMP criteria (113). Finally, criteria for success can be based on the improvement in comorbidities that often accompany obesity (106–108) (Table 2). An improvement in diabetes, fasting insulin, fasting glucose, or Hemoglobin A<sub>1c</sub>, insulin resistance, serum lipids, blood pressure, or disappearance of sleep apnea, and an improvement in the quality of life are all criteria that can be used to evaluate treatment outcome (112, 113). These criteria in modified form have been applied to data from eight randomized trials with fluoxetine (114). The authors conclude that they may be useful in comparing data across trials.

Criteria for evaluating weight loss drugs can calculate changes from the baseline weight (113) or as a difference from placebo (112). Figure 2 presents data from 10 clinical trials lasting from 10 to 26 weeks (wk) showing the variability

of the “placebo-group” (115–123, 123a). Assuming that the subjects averaged about 100 kg at the beginning of the trial, the numbers can be read as percentage weight loss. Weight losses in “placebo-treated” groups varied from less than 1% to nearly 9%. The multicenter trial reported by Walker *et al.* (124) is instructive (Fig. 3). The trial lasted 6 wk and compared mazindol to placebo. In four of the centers (*left panel*), the placebo group lost no weight, and the effect of mazindol was readily apparent. In the fifth center (*right panel*), all patients received “behavioral therapy” in addition to their group assignment of drug or placebo. In this setting the weight loss of the “placebo group” was similar to the weight loss in the other four treatment centers, and the weight loss produced by the drug was not significantly different. Reviews of the behavior therapy literature over the past 10 yr indicate that effective behavioral treatment can produce a weight loss of between 9% and 10% (125). Obviously, the “vigor” used in the placebo group can make a big difference. For this reason we prefer the CPMP criteria (113) to those of the FDA (112).

Figure 4 shows “placebo-group” responses in several clinical trials lasting from 31 to 60 wk. Again, note the diversity of responses (126–133). Most trials showed weight losses of more than 4 kg and one reached 14 kg. This variability in placebo response across trials of varying length reflects the inclusion of behavior therapy, diets with low or very low levels of energy, and exercise in the treatment plan in addition to the “placebo” pill. The problem with comparing a drug against these vigorous placebo effects can be appreciated from an analogy with treatment for hypertension. If patients with hypertension are given very-low-calorie diets with low-salt intake and increased calcium and magnesium intake and if they also abstained from alcohol and ate a high-fiber diet, it would be difficult to detect an additional effect of an antihypertensive drug. Similarly, if patients are losing weight rapidly with a behavioral program or a very-low-calorie diet, it may be difficult to see an additional effect of a medication that is designed as an appetite suppressant. Whether medications might make it easier to adhere to a very-low-calorie diet or a behavioral program is an unsettled question.

TABLE 3. Regulatory criteria for establishing efficacy of antiobesity drugs

	FDA criteria	CPMP criteria
<b>Early trials</b>		
Type of trial	Randomized, double-blind, placebo controlled dose ranging; identify lowest effective dose	Not specified
Duration	3–6 months	Not specified
Inclusion	BMI > 30 kg/m <sup>2</sup>	Not specified
Ancillary	Similar advice in diet, exercise, and behavior	Effective nonpharmacological therapy
1° Endpoint	Wt. loss significantly greater than placebo	Wt loss that is fat loss
No. patients	About 200, including both sexes and minorities	Not specified
Tolerability	Yes	Yes
Mechanism of action	Yes	Yes
Pharmacokinetics	Yes	Yes
Toxicology studies	Yes	Yes
Drug interactions	Yes	Yes
<b>Long-term</b>		
Type of trial	Randomized, double-blind, placebo controlled efficacy and safety	12 mo; open label or random 24 wk efficacy and safety
Duration	Year 1: double-blind Year 2: open-label or double-blind	At least 1 yr
Inclusion	BMI > 30 kg/m <sup>2</sup> of otherwise healthy or BMI > 27 kg/m <sup>2</sup> with comorbidities	BMI > 30 kg/m <sup>2</sup> of otherwise healthy or BMI > 27 kg/m <sup>2</sup> with comorbidities
Ancillary advice	Moderately restricted diet and exercise	Wt reducing diet; behavior modification; exercise
Run-in	Identify placebo responders; stratify; 6 wk	Yes
Measures	Body wt; body fat and fat distribution	Body wt: body fat and fat distribution
1° Endpoint	Wt. loss significantly greater than placebo and 5% > placebo at 12 mo Significantly greater no. achieving >5% wt loss	Wt. loss 10% below baseline and significantly > placebo at 12 mo Significantly greater no. achieving >10% wt loss
2° Endpoints	Maintenance of wt loss Significant change in body fat and fat distribution (may stratify—fat distribution risk factors, severity, duration, age) Improved cardiovascular risk factor Improved metabolic profile Improved quality of life	Maintenance of wt loss Improved biochemical parameters Reduction in cardiovascular risk Decreased blood pressure Decreased apneic episodes Loss of body fat and/or visceral fat Improved joint mobility Improved male and female infertility Improved quality of life
Subjects	Male and female; minorities About 1,500 to complete 12 mo with 200–500 completing 2 yr	Male and female

Rosner (134) has graphically summarized an approach to evaluating the success of weight loss (Fig. 5). The natural history of weight gain in the overweight is shown by the *dashed line* and represents an increase of about 0.25 kg/yr (135). A good population goal would be to prevent any further weight gain. For individuals who are overweight, a weight loss of 5% below baseline that is sustained would be the minimal criterion for success in this model. Weight loss of 5% to 10% with or without partial normalization of risk factors would be a fair response. A sustained weight loss of more than 10% with improvement in risk factors would be a good response. Weight loss in excess of 15% would be excellent, and normalizing of risk factors and reducing weight to a BMI below 25 kg/m<sup>2</sup> would be ideal, but is rarely achievable.

A new approach to evaluating weight loss has recently been proposed (136). It involves pattern analysis of longitudinal data. A pattern of interest is defined at the beginning of the trial and the proportion of patients meeting this are then evaluated. This approach has been used on one subgroup of a large multicenter drug trial (137).

With this wide variety of criteria to choose from, we calculated the percentage of initial weight lost and asked

whether it met the FDA criteria or the CPMP criteria. Among the clinical studies reviewed below, the maximal weight loss has usually been achieved by 20–24 wk. At 6, 12, and 18 wk, weight losses averaged 44%, 72%, and 89% of the weight loss at 24 wk. For this reason we have rarely included studies of 6 wk or less in the tables. We have generally included studies of more than 8 wk that were randomized and placebo controlled. In some instances, this was the first half of a 16-wk or longer cross-over study. We have rarely used data from the second half of cross-over studies because of the carry-over effects, and when this was done it will be noted.

### III. Physiological and Pharmacological Mechanisms to Reduce Food Intake

This section is the first of three different categories used in this review to classify treatments for overweight patients. Nutrients and monoamines can both reduce food intake and, in a smaller number of instances, increase food intake. Since many of these may provide clues to new approaches to treatment, most of the molecules in this category that influence feeding have been briefly reviewed.

FIG. 2. Weight loss of placebo-treated patients in clinical trials of antiobesity drugs lasting fewer than 30 weeks. [Adapted with permission from G. A. Bray: *Obes Res* 3:4255-4345, 1995 (108).]

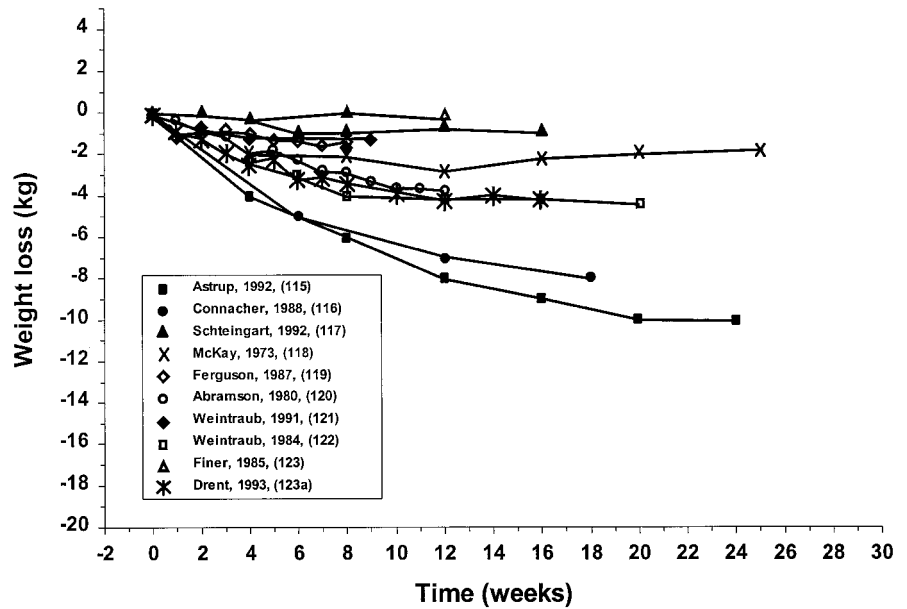
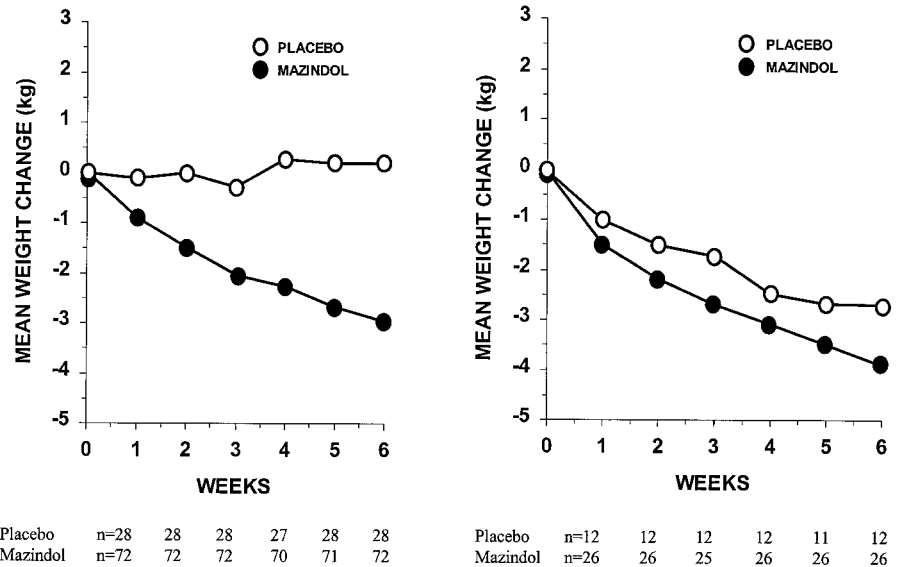


FIG. 3. Comparison of mazindol against placebo (left panel) or against placebo in combination with behavior modification given to all patients. [Adapted from B. R. Walker *et al.*: *J Int Med Res* 5:85-90, 1977 (124) by permission of Cambridge Medical Publications.]



A. Peripherally acting agents.

Most of the nutrients, monoamines, and peptides that alter food intake peripherally do so by decreasing food intake. These afferent signals are summarized in Table 4 and act primarily to produce satiety and restrain eating.

1. Nutrients.

a. Hexose analogs and metabolites. The glycostatic hypothesis (189), which might be better called the glucodynamic hypothesis (190), proposes that rates of glucose utilization or changes in glucose concentration may be signals to eat or stop eating. The most convincing data that glucose plays this role comes from Louis-Sylvestre and Le Magnen (191) and Campfield *et al.* (192) who have shown that a dip in glucose can precede and trigger the onset of eating in animals and human beings. Peripheral infusions of glucose decrease food intake in experimental animals (193); the vagus nerve may be

the connection between the peripheral glucoreceptors and the brain. When glucose is infused into the portal circulation, vagal afferent firing is reduced as the glucose concentration increases. Infusion of either glucose or arginine will lower the vagal firing rate and increase sympathetic efferent firing of nerves to brown adipose tissue (194).

5,7-Anhydro-mannitol (or deoxy-fructose) is an analog of fructose that stimulates food intake when given peripherally (139). One mode of action proposed for this compound is a decrease in hepatic ATP concentration. Another fructose analog (2,5-anhydromannitol) will stimulate food intake when given intracerebroventricularly (icv), but not when given intraperitoneally (ip) (140). The likely explanation for both compounds is their ability to interfere with glucose metabolism. Pyruvate and lactate, two metabolites of glucose, also decrease food intake when injected peripherally (150, 151). Analogs of these various metabolites might pose interesting

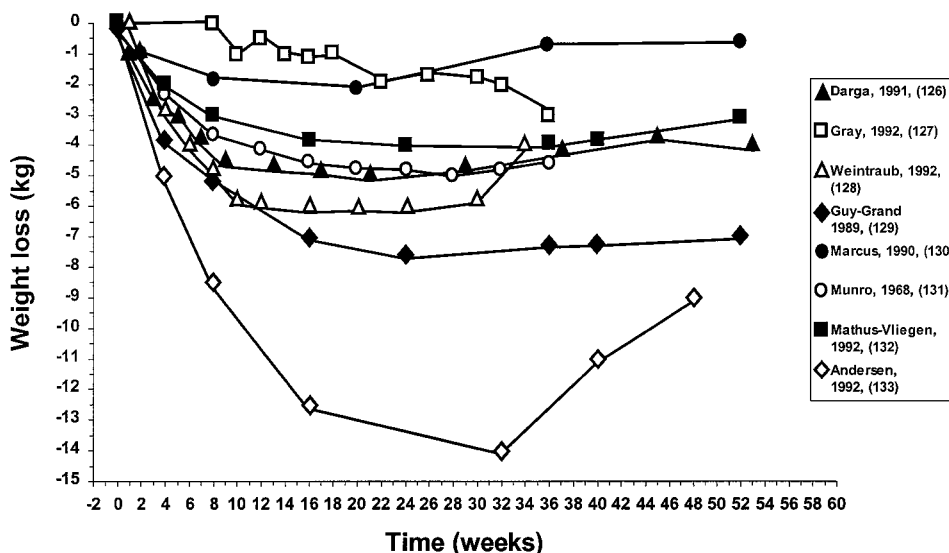


FIG. 4. Weight loss of placebo-treated patients in clinical trials of antiobesity drugs lasting 31–60 weeks. [Adapted with permission from G. A. Bray: *Obes Res* 3:4255–4345, 1995 (108).]

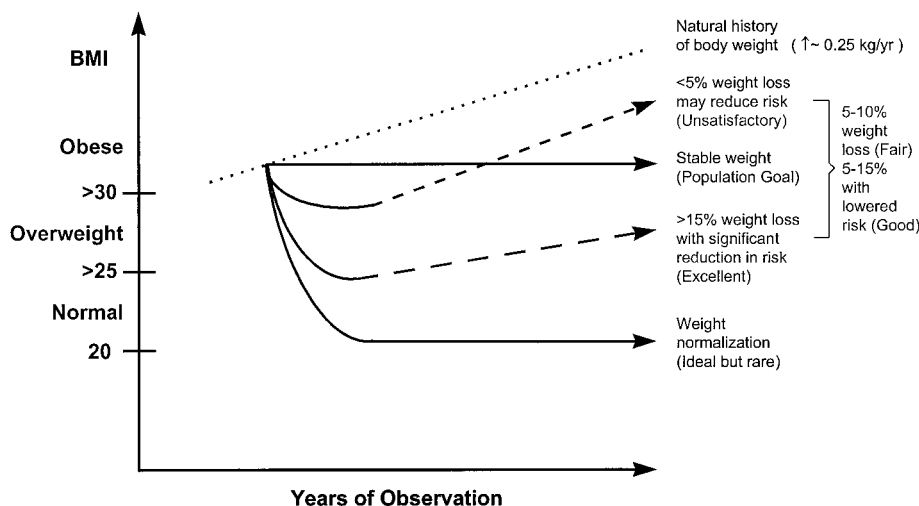


FIG. 5. An evaluation of treatment outcomes in relation to the natural history of obesity and the degrees of weight loss that can be achieved. [Adapted with permission from S. Rossner. In: *Obesity*, p. 712, 1992 (134) © Lippincott Williams & Wilkins.]

molecules to test for antiobesity effects. Glucosamine and *N*-acetylglucosamine both increase food intake when given orally to rats (140). The stimulation of feeding by *N*-acetylglucosamine was blocked by vagotomy, but the effect of glucosamine was only modestly attenuated. When glucosamine was given icv, it stimulated food intake. *N*-Acetylglucosamine, on the other hand, was without effect centrally. Fujimoto *et al.* (195) found that glucosamine accelerated lateral hypothalamic and decreased ventromedial hypothalamic neuronal activity.

Two other compounds deserve brief mention. The first are two polyphenols, gallic acid and its ester propylgallate (196). In feeding studies of lean and obese animals with ventromedial hypothalamic (VMH) lesions, propylgallate [propyl-(3,4,5-trihydroxybenzoate)] was more potent than gallic acid (196). The second compound is simmondsin, which is isolated from jojoba meal, an extract of *Simmondsia chinensis* that grows in the US Southwest (197). Simmondsin [2-(cyanomethylene)-3-hydroxy-4,5-dimethoxycyclohexyl-β-D-glucoside] decreases food intake within 1 h and remains effective when added to the diet. It may act through cholecystokinin<sub>A</sub> (CCK<sub>A</sub>)

receptors since devazepide blocked the effect of simmondsin (197).

*b. Ketones, fatty acids, and lipoproteins.* Intraperitoneal administration of 3-hydroxybutyric acid (3-OHB), a key metabolic product of fatty acid oxidation, decreases food intake (150, 157), and increased circulating levels of this metabolite have been proposed as a satiety signal (198, 199). The inhibition of food intake by 3-OHB is dependent on an intact vagus nerve since both vagotomy and capsaicin treatment, which destroys afferent vagal nerve fibers, block the inhibitory effects of 3-hydroxybutyrate on feeding (200).

Oomura and colleagues (143) have identified three endogenous fatty acid derivatives in the circulation of rats and humans that affect feeding. Two of these, 3,4-dihydroxybutanoate (201) and its lactam (2-buten-4-olide) (202, 203), are inhibitory of food intake. The third, 2,4,5-trihydroxypentanoate (204), stimulates feeding. Produced peripherally the most active stereoisomers are the 3-*S* isomer of 3,4-dihydroxybutanoate and the 2-*S*, 4-*S* isomer of 2,4,5-trihydroxypentanoate. The biological significance of the molecules that

TABLE 4. Compounds that affect food intake when given peripherally

	Effect on food intake	
	Increase food intake	Decrease food intake
<b>Monoamines and metabolites</b>		
2-deoxy-D-Glucose (138)		Glucose (140, 149)
2,5-Anhydromannitol (139, 140)		Lactate (150, 151)
Glucosamine (140)		Pyruvate (150, 151)
N-acetylglucosamine (140)		3-Hydroxybutyrate (150, 151)
1,5-anhydroglucitol (140)		3,4-Dihydroxybutanoate (143)
2-mercaptoacetate (141)		2-Buten-4-olide (143)
Methylpalmoxirate (142)		5-Hydroxytryptophan (152)
2,4,5-trihydroxypentanoate (143)		$\beta_2$ -Adrenergic Agonists (152)
		$\beta_3$ -Adrenergic Agonists (153–155)
		Serotonin (156, 157)
		Propylgallate (158)
		Simmondsin (159)
<b>Peptides</b>		
Insulin (144, 145)		Apoprotein IV (160)
$\beta$ -Casomorphin (146)		Bombesin (161, 162)
		Cholecystokinin (CCK) (163–167)
		Enterostatin (168–170)
		Glucagon (GLP-1) (171–175)
		Gastrin releasing peptide (176)
		Insulin (177)
		Leptin (178–182)
		Neuromedin B and C (183)
		Somatostatin (184)
<b>Steroids</b>		
Megesterol (147)		DHEA (185–186)
Medroxyprogesterone (148)		7-oxo-DHEA (187)
		Oleylestrone (188)

modulate neuronal activity in the lateral hypothalamus is unclear (205).

Inhibition of fatty acid oxidation by 2-mercaptoacetate (206), an inhibitor of acetyl-CoA dehydrogenase, or with methyl palmoxirate, (142, 207) an inhibitor of carnitine acyltransferase I, will increase food intake. Studies in animals indicate that this increased food intake is predominately carbohydrate and/or protein but not fat, even when fat is the only available nutrient (208). The peripheral effects of 2-mercaptoacetate are blocked by hepatic vagotomy but the effects of methyl palmoxirate are not (141, 209).

## 2. Monoamines.

*a. Norepinephrine (NE) and related compounds.* Peripheral injection of NE in experimental animals reduces food intake (149). Either  $\beta_2$ - and/or  $\beta_3$ -adrenergic receptors may mediate this effect. Treatment with  $\beta_2$ -adrenergic agonists will reduce food intake with little effect on thermogenesis (153). Clenbuterol was 10–30 times more potent than a  $\beta_1$ -agonist (dobutamine) or a  $\beta_3$ -agonist (ICI D-7114) in reducing food intake (153). However,  $\beta_3$ -agonists do acutely reduce food intake in lean and obese rats (210, 211) and in lean mice (155), but this effect is lost with continued treatment. In mice, knocking out the  $\beta_3$ -receptors in white fat blocks the reduction in food intake by  $\beta_3$ -agonists, indicating that there are peripheral  $\beta_3$ -adrenergic receptors involved in the modulation of food intake that act on fat cells, and possibly other tissues to produce inhibitory signals for feeding (155).

$\alpha$ -Adrenergic receptors are widely distributed and have many functions. During weight loss induced by diet, phen-termine, or fenfluramine, the  $\alpha$ -receptor binding by platelets of ligand NB4101 [2-([2', 6'-dimethoxy]phenoxyethylamin-o)methylbenzodioxan] was increased in all groups. The meaning of lower binding of  $\alpha$ -adrenergic receptors on platelets of obese subjects is unclear (212).

*b. Serotonin.* Peripheral injection of serotonin reduces food intake and specifically decreases fat intake (156, 213). Since the majority of serotonin is located in the GI tract, it may be that serotonin receptors in this tissue play an important role in the modulation of food intake, in response to enteral signals or to the rate of gastric emptying.

3. *Peptides.* CCK, bombesin, glucagon, insulin, enterostatin, cyclohistidyl-proline, somatomedin, amylin, leptin, and apoprotein IV (apo IV) all reduce food intake.  $\beta$ -Casomorphin is the only peptide known to us that increases food intake when administered peripherally. Of these, leptin, produced in adipose tissue, is one of the most important since it will reduce food intake and stimulate the sympathetic nervous system. CCK is the most clearly established GI peptide that is physiologically involved in suppression of food intake.

A number of peptides modulate feeding when injected peripherally (Table 4) (26, 27, 214–216). Table 5 pulls together information about all of the peptides that may be the basis for therapy aimed at strengthening the peripheral satiety messages. Each peptide will be discussed individually below. The table indicates by a Y for yes or N for no whether the effect has been documented for the peptide in question.

*a. CCK.* CCK-33 and the octapeptide of cholecystokinin (CCK-8) are produced in the GI tract (226). Two mechanisms exist to stimulate CCK release. The first is a so-called monitor peptide produced in pancreatic acinar cells and secreted into the intestine. The second is an intestinal factor (luminal CCK-releasing factor) that stimulates CCK release in response to ingestion of protein or fats or in response to protease inhibitors. This coordinate system (226–228) can regulate CCK levels in the GI tract. When injected parenterally, CCK-8 produces a dose-related reduction in sham feeding in experimental animals and in lean and obese human beings (164–167, 229, 230). There are two CCK receptors, CCK<sub>A</sub> and CCK<sub>B</sub>. The former is located primarily in the GI tract and the latter in the brain. CCK<sub>A</sub> receptor antagonists have been shown to increase feeding, implying that they may mediate a satiety signal from CCK. One hypothesis for this effect is that CCK acts on CCK<sub>A</sub> receptors in the pyloric channel of the stomach to cause constriction of the pylorus and to slow gastric emptying (231), suggesting an important role for this peptide-stimulated afferent pathway. The Otsuka Long-Evans Tokushima rat, which has no CCK<sub>A</sub> receptors, is obese and does not respond to exogenous CCK, which supports the physiological role of CCK (232).

Peptide analogs of CCK provide one avenue for drug development (233, 234). The recently described benzodiazepines that are CCK agonists are a second way to use this strategy (235). Antagonists to proteolytic degradation of CCK and CCK-releasing factors in the GI tract are a third approach to enhancing the effect of CCK and to altering



TABLE 5. Peptide targets for treatment of obesity

	CCK	Bombesin and neuromedin	GRP	Enterostatin	Glucagon and GLP-1	Leptin
Released by meals	Y	Y	Y	Y	Y	Y
Effective in rodents	Y	Y	Y	Y	Y	Y
Graded	Y	Y	Y	Y	Y	Y
Specific	Y	Y	Y	Y	Y	Y
Physiological	Y	Y	?	?	N(?)	Y
Effective in humans	Y	Y	Y	N	Y	Y
Graded	Y	?	Y	?	?	Y
Specific	Y	Y	Y	?	Y	Y
Physiological	Y(?)	?	?	?	Y(?)	Y
Blocked by antagonist						
Rat	Y	Y	?	?	Y	?
Human	Y(?)	?	?	?	N	?
Specific	Y(?)	?	?	?	?	?
References	163–167 217 218	161–162 219–221	176 222	168–170 223 224	171–175	178–182 225

Y, Yes, that effect is produced by peptide; N, no, that effect is not produced by peptide; ?, unknown or conflicting data.

gastric emptying, gastric distention, and food intake (226). Although acute treatment with CCK reduces food intake, chronic reduction in weight or food intake has only been shown by injecting CCK into animals that receive food during a restricted period of time (schedule fed) (27).

Vagotomy blocks the reduction in food intake produced by the peripheral injection of CCK, suggesting that afferent messages are generated in the gastroduodenal/hepatic circuit and relayed to the brain by the vagus nerve (27). These vagal messages initiated by the ip or iv administration of CCK activate several neuronal complexes in the brain including the nucleus of the tractus solitarius (NTS), the lateral parabrachial nucleus, and the central nucleus of the amygdala, as assessed by expression of the early gene product *c-fos* (236). The production of early satiety by CCK does not require an intact medial hypothalamus because it occurs in human beings with hypothalamic injury and obesity (167).

In human studies CCK reduces food intake by 6–63% (average 27%) in lean subjects and 13–33% (average 21%) in obese subjects. A small number of studies have reported GI side effects (27).

In addition to its peripheral effects, CCK injected into the central nervous system (CNS) will also decrease food intake (237) and increase sympathetic activity (238) by acting through CCK<sub>B</sub> receptors. A biological role for CCK in the brain in modulating feeding is suggested by the fact that food in the stomach is associated with the release of CCK in the hypothalamus and that blockade of CCK in the brain with anti-CCK antibodies increases food intake (229).

*b. Bombesin, neuromedin B and C, and gastrin-releasing-peptide (GRP).* Bombesin is a tetradecapeptide that was isolated from amphibian skin and is similar in structure to mammalian GRP and neuromedin B (Table 4) (215). Bombesin acts through three different receptors, a GRP receptor, a neuromedin B receptor (239), and a bombesin-3 receptor. Studies on the contractile effect of bombesin in the gastric fundus shows bombesin to be more potent at binding to the GRP-preferring receptors than either neuromedin B or neuromedin C (240). The suppression of food intake showed the following order of potency: bombesin = acetyl neuromedin

C > neuromedin C = gastrin releasing peptide > neuromedin B = acetylneuromedin B (241). A mouse with a knock-out of the bombesin-3 receptor has been reported to be moderately obese after at least 6–8 wk of age (242). Hyperphagia, however, is only a significant feature at greater than 12 wk after the obesity has developed, suggesting that at least one of the three bombesin receptors may be involved in regulation of long-term fat stores.

Administration of bombesin parenterally to experimental animals or iv to human beings (161, 162, 221, 243) will reduce food intake but, in contrast to CCK, this effect is not completely blocked by vagotomy although it can be blocked by vagotomy and interruption of spinal afferents (244, 245) (Table 5). The effects of bombesin are independent of CCK since drugs that block the effects of CCK do not block bombesin. Bombesin (161, 162) and GRP (176) decreased food intake in lean humans but not in obese women compared with saline (221).

GRP has 27 amino acids and inhibits food intake in rats (222) (Table 5). It also reduces food intake in human beings (176). In addition to the peripheral receptors for GRP, GRP receptors in the hindbrain are also necessary for the peripheral response to GRP (243).

Peripheral or central injection of bombesin reduces food intake that is not blocked by vagotomy (244, 245). Bombesin also activates the sympathetic nervous system (249). In animals that have been starved or have ventromedial hypothalamic lesions, bombesin produces a profound drop in temperature because the sympathetic nervous system cannot be activated (249). In intact animals, bombesin will reduce body temperature if a ganglionic blocking drug or the  $\beta$ -adrenergic antagonist, propranolol, is given that will eliminate the sympathetic activation of the thermogenic system in brown adipose tissue by bombesin.

*c. Glucagon.* Glucagon is a 29-amino acid peptide that reduces food intake after peripheral administration (173, 250) (Table 5). It produces a dose-dependent inhibition of food intake after portal vein administration in experimental animals. Antibodies that bind glucagon increase food intake, suggesting that the signals generated by pancreatic glucagon

act in the liver and may be physiologically relevant in modulating feeding. Glucagon decreases food intake in human beings, but this does not occur if glucagon and CCK are given simultaneously (174).

Glucagon like peptide-1 (glucagon 6–29) is produced by the posttranslational processing of proglucagon and is thought to be one signal to enhance insulin release in response to glucose incretin (251). Infusion of glucagon-like peptide 1 (GLP-1) peripherally in human subjects will significantly reduce food intake (175). (The central actions of GLP-1 are discussed below.)

*d. Insulin.* The effects of insulin on food intake depend on the dose and route of administration. Although intraportal infusion of insulin did not affect food intake in rats, infusion of an antiinsulin antibody increased meal size suggesting that the presence of insulin may be related to meal termination (252).

In doses that will lower blood glucose, insulin is hyperphagic probably because it produces hypoglycemia (144, 145). Indeed the transient declines in glucose that precede many meals may result from a brief transient rise in insulin (192). In contrast, chronic infusion of low doses of insulin inhibit feeding (177). Infusion of insulin into the ventricular system decreases food intake and body weight of baboons (253) and rodents (198, 254–257). This occurs in animals eating a high-carbohydrate diet but not in those eating a high-fat diet (198). Schwartz and colleagues demonstrated that changes in cerebrospinal fluid insulin reflect blood levels and are related to food intake (257). They showed that the entry of insulin is a facilitated process and that it may be a negative feedback for regulating fat stores. A low level of insulin secretion and enhanced insulin sensitivity both predict weight gain in Pima Indians (258, 259).

Diazoxide is one approach to lowering insulin and is successful in slowing weight gain in animals (260). Long-term octreotide treatment has caused weight loss, reduced insulin resistance, and reduced acanthosis nigricans in a case report (261, 262). An agent that reduces insulin secretion and obesity in experimental animals has been reported by Campfield *et al.* (263) and opens the field to new potential agents.

*e. Enterostatin and cyclohistidyl-proline (c-HP).* Enterostatin (val-pro-gly-pro-arg) is a pentapeptide produced by trypsin cleavage of pancreatic procolipase in the intestine (223, 264) (Table 5) and appears in chromaffin cells in the stomach as a result of local synthesis or accumulation of circulating enterostatin (265). Procolipase is secreted in response to dietary fat and its signal peptide, enterostatin, is highly conserved across a number of species (170, 223). Enterostatin decreases food intake whether given peripherally or centrally (168–170). Injection of enterostatin peripherally selectively reduces fat intake by nearly 50% in animals that prefer dietary fat (169, 170). The peripheral effects of enterostatin are blocked by vagotomy or capsaicin treatment, indicating the importance of afferent vagal information for the action of this peptide (266). This afferent information activates *c-fos* expression in the nucleus of the NTS, in the lateral parabrachial nucleus, the central nucleus of the amygdala, and the supraoptic nucleus (266), which is similar to CCK. Injection

of enterostatin also enhances serotonin turnover in the CNS (223). The dose-response curve for enterostatin is U-shaped with an optimal inhibitory effect on feeding in rats being at 1 nmol peripherally. Higher and lower doses are less effective, and at high doses enterostatin actually stimulates food intake. Enterostatin stimulates the sympathetic nervous system at doses that decrease food intake (248), and chronic infusion will reduce body weight (267).

Enterostatin reduces food intake by icv injection just as it does when given peripherally. It selectively reduces fat intake and is more potent when injected in the amygdala than in the paraventricular nucleus (PVN) (268). There is almost no response when enterostatin is injected into the NTS (268). At high doses in nondeprived rats, enterostatin has been reported to increase food intake (269). In one clinical trial the administration of enterostatin iv did not reduce food intake in humans (224).

*f. Somatostatin (SRIF).* SRIF is a 14-amino acid peptide that is present in the pancreas, GI tract, and brain. SRIF serves to inhibit GI motility as well as exocrine and endocrine secretions (Table 4). In experimental animals it decreases food intake (270). SRIF also decreases food intake in healthy human beings (184). During the first hour of SRIF infusion there was a significant decrease in feelings of hunger. When an intraduodenal fat load was given at this time, it tended to reverse the feelings of satiety. The intake of sandwiches 90 min after the fat load tended to be higher during the SRIF than during the saline infusion. Feelings of hunger were less in the 5 h after terminating the SRIF infusion than with the control infusion.

*g. Amylin.* Amylin or islet-associated polypeptide, is a 37-amino acid peptide that is cosecreted with insulin from the pancreatic  $\beta$ -cell. Many of its biological activities mimic those of the calcitonin gene-related peptide that is not a  $\beta$ -cell peptide (271). The level of amylin is related to the level of insulin and is higher in older, somewhat more obese, animals than in lean animals (272). The ratio of amylin to insulin is increased in genetically obese animals. In individuals with Type I insulin-dependent diabetes, amylin is essentially absent from the plasma. The plasma level of amylin rises after a meal or a glucose load (271). In a transgenic mouse overexpressing amylin, plasma levels were increased 15-fold, but there was no elevation in glucose or insulin and obesity did not develop (273). Amylin will decrease food intake in mice (274, 275) and rats given either peripherally (276) or intrahypothalamically (277). At present, we were unable to locate any studies on food intake with amylin in humans.

*h. Leptin.* Leptin was discovered by cloning the *ob* gene in the obese hyperglycemic mutant mouse, which is a widely studied model of diabetes and insulin resistance. It is a 167-amino acid peptide whose receptor is a member of the gp 130 cytokine superfamily (178–182). Since its discovery in 1994 (278), there has been a logarithmic increase in publications about this peptide (182). Leptin is synthesized and secreted primarily from adipocytes, but can also be made by the placenta. Circulating levels of leptin are highly correlated with the level of body fat. Leptin production by adipocytes is stimulated by insulin and glucocorticoids, and it is inhib-

ited by  $\beta$ -adrenergic stimulation (181, 182, 279). Circulating leptin may be bound to a "carrier" protein. Deficiency of leptin in mice (278) and in humans (280) is associated with massive obesity. Conversely, chronic administration of leptin to animals or overexpression of leptin in transgenic mice (281) reduces body fat in a dose-related manner. Leptin reduces food intake and increases the activity of the sympathetic nervous system.

These effects of leptin occur through leptin receptors. Several variants of the leptin receptor have been identified and cloned. In the brain the long form of the leptin receptors ( $R_b$ ) is located in the medial hypothalamus. Activation of leptin receptors produces stimulation of Janus kinase (JAK), which activates signal transduction and translation (STAT) signal molecules. Absence of the leptin receptor produces obesity in mice and in humans (282). The interaction of leptin with receptors in the brain activates neurons in the arcuate (ARC) nucleus that produce POMC, and coordinately reduces activity of ARC nuclei producing neuropeptide-Y (NPY) (181, 182). These two peptide systems are believed to mediate the effects of leptin on food intake in the CNS. Lesions in the ventromedial hypothalamus abolish the effects of leptin (287).

The receptor subunits of leptin share sequence similarities with the hypothalamic receptor for ciliary neurotrophic factor (CNTF), a neurocytokine (283). Leptin and CNTF produce similar patterns of activation of STATs. Treatment with CNTF of either *ob/ob* mice, which lack leptin, or *db/db* mice, which lack the leptin receptor, reduced the adiposity, hyperphagia, and hyperinsulinemia. CNTF was similarly effective in mice with diet-induced obesity. These findings coupled with the fact that the overexpression of leptin in transgenic mice will almost completely eliminate body fat suggests that this system may be a valuable one to target. In a published trial using CNTF in patients with amyotrophic lateral sclerosis (284), weight loss and anorexia were among the most notable side effects.

Data from one clinical trial with leptin were published in 1999 (225). A total of 54 lean (72 kg) and 73 obese subjects (90 kg) were assigned to 4 wk of treatment with three daily injections of r-metHuLeptin at doses of 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, or 0.3 mg/kg and were randomized within each dose level to placebo or leptin and stratified according to BMI (227). At the end of 4 wk, 60 of the 70 obese patients who remained in the study elected to continue for an additional 20 wk. Subjects were on a 500 kcal/day below maintenance diet throughout the study. Using subjects who completed the study ( $n = 53$  lean at 4 wk and  $n = 47$  obese at the end of 20 wk), the authors found a significant dose-response effect for weight loss from baseline at 4 wk and from baseline in the obese subjects treated for 24 wk (weight changes for obese subjects at 24 wk were  $-1.7$  kg for placebo;  $-0.7$  kg at 0.01 mg/kg;  $-1.4$  kg at 0.03 mg/kg;  $-2.4$  kg at 0.10 mg/kg; and  $-7.1$  kg at 0.3 mg/kg). Injection site reactions were the most common adverse event, but only two subjects withdrew for this reason. Glycemic control was unchanged during the study. Leptin treatment of a child with leptin deficiency also lowered food intake and body weight (225a). These studies show that human leptin can produce weight loss

in human beings. The route of delivery needs to be improved if it is to become acceptable.

*i. Apo IV.* Apo IV is produced by the intestine and is incorporated into lipoproteins and chylomicrons. When this peptide is injected peripherally, there is a significant decrease in food intake. The release of apo IV during the hydrolysis of lipoproteins by lipoprotein lipase in the periphery has been hypothesized to be a satiety signal related to fat digestion (160, 285). The active component of apo IV is a short amino acid sequence that may provide new clues for peripherally acting agents that can reduce food intake.

*j.  $\beta$ -Casomorphin.*  $\beta$ -Casomorphin is the only peptide that stimulates food intake when given peripherally. It is a cleavage product of milk casein (146). It has seven amino acids with the sequence *Y-P-F-P-G-P-I* (Tyr-pro-phe-pro-gly-pro-ileu) in contrast to the *V-P-D-P-R* (Val-pro-gly-pro-arg) or *A-P-G-P-R* (ala-pro-gly-pro-Arg) sequences for enterostatin. Because of the P-X-P similarities between enterostatin and  $\beta$ -casomorphin,  $\beta$ -casomorphin and its four and five amino acid N-terminal fragments were tested on food intake (146).  $\beta$ -Casomorphin 1-7 stimulates food intake when injected peripherally. This effect is completely lost if the three carboxy-terminal amino acids G-H-I, are removed. However,  $\beta$ -casomorphin 1-4 still retains its opioid-like properties. Thus, the G-H-I (Gly-His-Ileu) carboxy-terminal tripeptide contains important information for modulating feeding.

### B. Centrally acting agents

A number of metabolites and peptides can act within the CNS to modulate food intake. These are summarized in Table 6. Where they are discussed depends primarily on where they originate.

*1. Nutrients.* The same nutrients that modulate feeding peripherally may also act in the CNS. Inhibition of glucose utilization with 2-deoxy-D-glucose increases feeding, showing that central glucose utilization modulated feeding. The effects of 5-thioglucoase, gold thioglucoase, and phlorizin (an inhibitor of glucose transport) also increase food intake. Of the amino acids,  $\gamma$ -aminobutyric acid (GABA) can stimulate or inhibit feeding, depending on which hypothalamic nucleus it is injected into. Glutamate injected into the perifornical area also stimulates feeding. An antiepileptic drug, valproate, which may work on the GABA receptors, produces significant weight gain in many individuals.

*a. Glucose and glucose analogs.* The injection of glucose into the ventricular system of the brain in doses ranging from 2 to 30  $\mu$ mol has been shown to reduce food intake in some experiments (288, 316) but not others (330). The presence of glucoreceptors in the hypothalamus (331) suggests that glucose in the CNS may play a role in modulation of feeding, although these receptors may be involved in other processes as well. Glucose injected into the third cerebral ventricle increases sympathetic firing rate to brown adipose tissue showing a functional role for hypothalamic glucoreceptors in the reciprocal relationship of food intake and the activity of the CNS (332).

TABLE 6. Compounds that affect food intake when given into the central nervous system

Effect on food intake	
Increase food intake	Decrease food intake
<b>Monoamines and metabolites</b>	
NE( $\alpha_2$ ) (clonidine) receptors (210)	NE ( $\alpha_1$ ; $\beta_2$ ) (307, 308)
$\gamma$ -Aminobutyric acid (GABA) (286)	Serotonin (5-HT <sub>1B</sub> or 2C) (309)
2-Deoxy-D-glucose (287, 288)	Dopamine (310)
5-Thiogluucose (289)	Histamine (311, 312)
Goldthiogluucose (290, 291)	GABA (286)
Bipiperidyl mustard (292)	3-Hydroxybutyrate (198, 313, 314)
4-Nitroquinoline-1-oxide (293)	Glutamate (315)
Phlorizin (288, 294)	Glucose (288, 316, 317)
Monosodium glutamate (295, 296)	5-Hydroxytryptophan (152, 318)
Procaine (297)	
Colchicine (298)	
<b>Peptides</b>	
Dynorphin (299)	Apoprotein IV (285)
$\beta$ -Endorphin (300)	Calcitonin (CGRP) (319, 320)
Galanin (301)	CART (cocaine-amphetamine regulated transcript) (321)
GH releasing hormone (302)	CRH/urocortin (322–324)
Melanin concentrating hormone (303)	Cyclo-his-pro (325)
Neuropeptide-Y (304)	GLP-1 (326)
Orexin A and B (hypocretin) (305, 306)	Insulin (198, 253–255)
	Neurotensin (327)
	$\alpha$ -MSH (328, 329)

Several analogs of glucose have been used to explore further the role of glucose in feeding (Table 4). 2-Deoxy-D-glucose (2-DG) is an analog of glucose that is transported into cells and phosphorylated but not further metabolized (287, 288). This metabolite blocks metabolism of glucose-6-phosphate and produces intracellular glucopenia that stimulates food intake in experimental animals and human beings whether injected into the CNS or peripherally (138, 287, 288, 333).

2-DG increases food intake, inhibits sympathetic activity to brown adipose tissue, and increases the firing rate of the adrenal nerves, which increase epinephrine secretion (138, 334). The hyperglycemia produced by 2-DG can be blocked by adrenalectomy, indicating that it is epinephrine release and the ensuing hepatic glycogenolysis that raises plasma glucose. Food consumption induced by 2-DG can be antagonized by injecting amphetamine into the PVN (335). Using the expression of the gene product *c-fos*, peripheral injection of 2-DG was shown to activate a number of neuronal groups in the brain including the nucleus of the NTS, the lateral parabrachial nucleus, and the central nucleus of the amygdala. Selective peripheral hepatic vagotomy does not block the activation of *c-fos* by 2-DG, suggesting that the major site for action for 2-DG may be in the hindbrain (141, 209). The stimulation of food intake by 2-DG may involve GABA receptors since injection of picrotoxin, an antagonist of GABA<sub>A</sub> receptors, will block the stimulation of food intake by 2-DG (288).

5-Thiogluucose is a second glucose analog that will impair the metabolism of central or peripheral glucose and stimulate food intake. This analog was used by Ritter and co-workers (206, 289) to show the presence of glucose receptors in the hindbrain.

Gold thiogluucose is a third glucose analog that affects food intake. It is transported into the hypothalamus where the gold deposits damaging neuronal tissue and leads to hyperphagia and obesity (290, 291).

Phlorizin, a competitive inhibitor of glucose transport, increases food intake when injected into the cerebroventricular system (288, 294, 317), again suggesting a role of brain glucose in modulating feeding.

The brain contains a receptor system similar to the sulfonylurea receptor in the pancreatic  $\beta$ -cell. This receptor is a K<sup>+</sup> ATP channel that is closed by the ATP produced during glucose metabolism. Sulfonylurea drugs have similar effects (335–337). Modulation of this receptor may provide a way of enhancing and/or manipulating food intake. A difference in the low-affinity sulfonylurea receptor in rats sensitive to dietary-induced obesity has recently been reported by Levin *et al.* (338), making this an intriguing hypothesis. Recent studies from several laboratories, however, have produced evidence that the sulfonylurea receptor is involved in human diabetes (339–341). Hani *et al.* (342) observed a significant association between the exon 22 T genetic variant of the low-affinity sulfonylurea receptor and morbid obesity in two groups of patients.

*b. Fatty acids and ketones.* Infusion of 3-hydroxybutyrate into the brain's ventricular system will depress food intake in lean animals independent of diet (198, 312, 313). Infusion of 3-hydroxybutyrate significantly reduces food intake and body weight and increases sympathetic activity (313). These effects of ketones in the CNS are consistent with the observations of Oomura *et al.* (343) showing the presence of fatty acid-responsive neurons in the lateral hypothalamus.

*c. Amino acids.* Administration of 5-hydroxy tryptophan to obese and diabetic subjects (152, 318) will decrease food intake probably by enhancing brain tryptophan, which is converted to serotonin, a neurotransmitter known to reduce food intake. Tryptophan is transported across the blood brain barrier by a transporter that also transports other large neutral amino acids. When these other amino acids are in-

creased, tryptophan entry is reduced by competition for the transporter.

Amino acids in the CNS can be excitatory or inhibitory. Glutamic acid serves as a general neuronal excitatory amino acid and GABA and glycine serve as general inhibitory amino acids. Glutamate infusion into the perifornical area of the hypothalamus increases food intake and body weight (315).

GABA may either increase or decrease food intake depending on its site of action. Microinjection of GABA in the medial hypothalamus increases food intake, whereas inhibition of food intake occurs when it is given into the lateral hypothalamus (286). Antagonists of GABA, such as picrotoxin or bicuculline, can block the stimulation of feeding produced by 2-DG (286), suggesting that GABA-ergic neurons make up one part of this circuit. Monosodium glutamate, a flavor enhancer, will damage hypothalamic neurons when injected into neonatal rats. This is followed by an obesity that develops without significant hyperphagia but with a decrease in sympathetic activity (344). MK-801, a noncompetitive *N*-methyl-D-aspartate agonist, has been reported to increase food intake (345). Several neuroactive steroids of the 3- $\alpha$ -hydroxy ring-A-reduced pregnane series have also been found to be antagonists of GABA<sub>A</sub> receptors and may have potential in modulating food intake (346).

A potential clinical role for drugs working on GABA or glutamate neurotransmitters is suggested by studies on drugs developed to treat epilepsy. Valproate, which acts on GABA receptors, produces weight gain in the majority of treated patients (347). Topiramate, another antiepileptic drug that also acts on GABA receptors, produces a dose-related decrease in body weight. Although the precise mechanism of action is not known, topiramate appears to block voltage-dependent sodium channels. It also enhances the activity of GABA<sub>A</sub> receptor, and it antagonizes a glutamate receptor other than the *N*-methyl-D-aspartate glutamate receptor. At doses less than 200 mg/day, weight loss was 1.7% (1.3 kg) and rose to 7.2% (6.1 kg) in patients receiving more than 800 mg/day. The weight loss was evident by 3 months and continued beyond 6 months. Although some regain occurred, 50 patients treated for 60–66 months were 3.3 kg below baseline (348).

**2. Monoamines.** All of the major monoamines, including NE, serotonin, dopamine, and histamine, modulate feeding. Depending on the receptor systems activated, they can either increase or decrease food intake. Activation of the serotonin 1A receptor or the NE-activated  $\alpha_2$  receptor or the histamine-3 autoreceptor can increase feeding. Activation of the other receptors by NE, serotonin, dopamine, or histamine reduces food intake.

*a. NE.*

*i) Adrenergic receptors:* The importance of central NE in the regulation of food intake is suggested by three observations. First, lesions of the ventral noradrenergic bundle, which abolishes NE release in the perifornical area, is associated with weight gain (349). This lesion also blocks the anorectic effect of amphetamine and diethylpropion (350). Second, blockade of tyrosine hydroxylase by injecting  $\alpha$ -methyl-*p*-tyrosine into the perifornical area increases feeding by block-

ing NE synthesis (351). And, finally, infusion of NE into the VMN can increase food intake, decrease sympathetic activity, and produce obesity (352). This allows two strategies for drug discovery. The first is to design agonists that are specific for the desired receptor or receptors. The second is to block reuptake of NE in regions where the increased NE pool will have the desired effect on food intake.

NE can increase or decrease food intake depending upon the type of adrenergic receptors on which it acts in the brain (308). NE acting on  $\alpha_1$ -adrenergic receptors in the PVN decreases food intake. Adrenergic agonists such as phenylpropanolamine (PPA) or metaraminol will reduce food intake (354). This effect is blocked by injection of  $\alpha_1$ -adrenergic antagonists (354). That the  $\alpha_1$ -adrenergic system is involved in modulating body weight in human beings is suggested by the fact that the  $\alpha_1$ -adrenergic antagonist terazosin, which is used to treat hypertension, is associated with small weight gains relative to placebo in double-blind randomized placebo-controlled trials (355).

There are three  $\alpha_2$ -adrenergic receptors ( $\alpha_{2A}$ ,  $\alpha_{2B}$ , and  $\alpha_{2C}$ ) that are coupled through G proteins to modulate cAMP and calcium channels. Activation of  $\alpha_2$ -adrenergic receptors in the PVN by NE or by clonidine in experimental animals (210, 353) will stimulate food intake. This effect can be blocked by  $\alpha_2$ -adrenergic antagonists such as yohimbine or idazoxan. Clinically, neither clonidine nor yohimbine has any significant or consistent effects on body weight in humans (356).

NE stimulation of  $\beta_2$ -adrenergic receptors located in the perifornical area will decrease food intake (308, 353).  $\beta_2$ -Agonists such as clenbuterol and salbutamol will decrease food intake when injected into the CNS (210). Injection of  $\beta_3$ -agonists into the CNS also decreases food intake (210). Whether this is through  $\beta_3$ -receptors in the CNS or by action on  $\beta_2$ -receptors in the CNS or  $\beta_3$ -receptors peripherally remains to be determined (153–155).

*ii) Mechanism of activating adrenergic receptors:* Receptor agonists are one mechanism to activate this system. PPA is an  $\alpha_1$ -agonist that reduces feeding (354). Clonidine is an  $\alpha_2$ -agonist that stimulates food intake in experimental animals. A number of  $\beta_2$  agonists inhibit feeding (153, 210). Alternatively, drugs can block reuptake of NE (357). Mazindol is a tricyclic drug that is thought to block reuptake of NE. However, a highly specific NE reuptake inhibitor, nisoxetine, alone does not increase food intake, suggesting that either NE alone is insufficient to affect feeding or that the NE reuptake blocked by nisoxetine is acting in the wrong place (358). Direct application of NE to the hypothalamus is sufficient to stimulate feeding (306). The final way to enhance interneuronal NE is to enhance NE release. Amphetamine, phentermine, and diethylpropion are thought to act by this mechanism (357) but they may also act as inhibitors of NE and dopamine reuptake.

*b. Serotonin.*

*i) Serotonin receptors:* There are seven different families of serotonin receptors [5-hydroxytryptamine (5-HT)] with several receptor subtypes in some of these families (359). Most of these subtypes are in the 5-HT<sub>1</sub> and 5-HT<sub>2</sub> series. These receptors may mediate the reduction of food intake that occurs when serotonin agonists such as quipazine, meta-

chlorophenylpiperazine (mCPP) and *d*-norfenfluramine are injected into the PVN (360). The signal transduction system for most of the serotonin receptors involves G-coupled activation or inhibition of adenylate cyclase. The 5-HT<sub>3</sub> receptor is the exception, acting through an ion channel (359).

Serotonin is clearly involved in regulation of food intake (157, 361), and several serotonin receptors have been implicated in this process. Activation of the 5-HT<sub>1A</sub> receptor, an autocrine receptor in the dorsal raphe nucleus, acutely stimulates food intake (362). Acute administration of flesinoxan, a 5-HT<sub>1A</sub> agonist in doses of 10 mg/kg to rats increases food intake and NPY levels in the PVN and ARC nucleus (363). However, chronic administration of 5-HT<sub>1A</sub> receptor agonists down-regulates 5-HT<sub>1A</sub> receptors and no longer stimulates feeding.

Stimulation of the 5-HT<sub>1B</sub> receptor reduces food intake by acting at a postsynaptic receptor. Knock-out of the 5-HT<sub>1B</sub> receptor (364) blocks the reduction of food intake by fenfluramine, suggesting that this receptor plays an important role in modulating feeding (365). A 5-HT<sub>1B/2C</sub> agonist, mCPP, reduced food intake and NPY levels in the PVN, both acutely and after 7 days of administration at 10 mg/kg to rats (363). Stimulation of the 5-HT<sub>2C</sub> receptor through its G protein-coupled receptor activates phospholipase C, which produces two intracellular signals, inositol 3-phosphate and diacylglycerol. Transgenic mice lacking the 5-HT<sub>2C</sub> receptor (366) show increased epilepsy and weight gain, suggesting that this receptor, also, may be involved in regulating food intake (367). The 5-HT<sub>3</sub> receptor activates an ion channel and may be involved in the anorectic response to diets deficient in single amino acids (368). A comparison on food intake of antagonists to the 5-HT<sub>1B</sub>, to the 5-HT<sub>2A/2C</sub> receptor, and to the 5-HT<sub>3</sub> receptor concluded that the 5-HT<sub>1B</sub> and the 5-HT<sub>2A/2C</sub> receptors were most involved with food intake (369).

*ii) Mechanisms activating serotonin receptors:* Drugs that block serotonin reuptake, such as fluoxetine and sertraline, significantly decrease food intake (370). The effect of fluoxetine on food intake is not inhibited by metergoline, suggesting that this effect may be by some mechanism other than serotonin. In a manner analogous to NE, the serotonin receptors modulating feeding can be activated by receptor agonists by enhancing serotonin release or blocking serotonin reuptake. A number of serotonin receptor agonists have been synthesized to explore the serotonin receptor system as a target for antiobesity drugs (371). So far, none have reached clinical trials.

Drugs such as dexfenfluramine that release serotonin and act as partial reuptake inhibitors also decrease food intake (372). These inhibitory effects of dexfenfluramine are attenuated by metergoline, a broad-spectrum serotonin antagonist (373). The effect of dexfenfluramine can also be blocked by serotonin reuptake inhibitors. Reduction of food intake by dexfenfluramine is also blocked by lesions in the lateral parabrachial nucleus (374).

*c. Dopamine receptors.* At least five dopamine receptors have been identified (310). D<sub>1</sub> and D<sub>5</sub> are very similar as are D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub>. Drugs acting on these groups of receptors can alter food intake but may also be associated with a variety of

effects on mood. Agonists to the two main dopamine receptors differ. D<sub>1</sub>/D<sub>5</sub> agonists reduce the duration of feeding primarily by decreasing the frequency of feeding episodes. D<sub>2</sub> agonists, on the other hand, reduce the rate of eating (310). Sulpiride is an antagonist of the dopamine D<sub>1</sub> receptor and increases food intake (376). Apomorphine is a D<sub>1</sub>/D<sub>5</sub> agonist that decreases food intake (375). *d*-Amphetamine may act, in part, as a dopamine reuptake inhibitor.

Bromocriptine (Novartis, East Hanover, NJ), a specific D<sub>2</sub> agonist, has been reported to decrease body weight in obese subjects (377). Bromocriptine has been used for treatment of PRL-secreting adenomas without reported changes in body weight. Based on studies on experimental animals in which PRL secretion was associated with fat storage in migratory birds and prehibernating mammals (378), a clinical trial was conducted (379). Bromocriptine, administered in appropriately timed doses, was claimed to reduce skinfold thickness and weight relative to placebo. Its role in clinical treatment of obesity is currently being assessed (377).

*d. Histamine receptors.* Experimentally, histamine H<sub>1</sub> and H<sub>3</sub> receptors in the CNS have been implicated in the modulation of food intake (311, 312). The H<sub>3</sub> receptor is an autoreceptor through which histamine inhibits the release of histamine at nerve terminals (311, 380). An H<sub>3</sub> antagonist, thioperamide, suppressed food intake by blocking this autoreceptor and thus releasing histamine. The decrease in food intake by thioperamide could be blocked by an H<sub>1</sub> antagonist chlorpheniramine, which prevented histamine that was released from acting on its H<sub>1</sub> receptor. Depletion of neuronal histamine by destroying histamine decarboxylase with  $\alpha$ -fluorohistadine increases food intake, suggesting histamine acting through H<sub>1</sub> receptors is an inhibitory monoamine. Ionophoretic application of an H<sub>1</sub> antagonist into the PVN/VMH blocked the rise in food intake produced by depleting neuronal histamine. An H<sub>2</sub> antagonist, on the other hand, was without effect (311, 380).

Two reports in obese human beings using cimetidine, an H<sub>2</sub>-blocking drug, have produced contradictory data (381, 382). In one report, obese patients treated with 200 mg cimetidine, 30 min before meals, three times a day, lost 7.3 kg more than the placebo-treated patients over an 8-wk period (381). In a second study that also contained 60 subjects treated with the same dose of cimetidine over 8 wk, no difference in weight loss was seen between cimetidine-treated and placebo-treated patients (382). The question of whether blockade of histamine H<sub>2</sub> receptors will produce weight loss is thus unclear (383). Some of the weaker neuroleptics, such as chlorpromazine, thioridazine, and mesoridazine, may increase body weight by acting on histamine receptors as well as serotonin receptors.

*3. Drugs acting through central monoamine receptors.* The pharmacology of drugs acting through the monoamine system are summarized. Whether acting on noradrenergic receptors or serotonergic receptors, these drugs reduce food intake. Some of them also increase thermogenesis. These drugs are rapidly absorbed. The duration of clinical effect depends on the metabolites. Both dexfenfluramine and serotonin have long-lasting metabolites. The noradrenergic drugs can produce stimulation of the CNS and cardiovascular system. A

number of metabolic and endocrine effects have also been described.

*a. Experimental pharmacology.* All of the centrally acting anorectic drugs, except for mazindol, are derivatives of  $\beta$ -phenylethylamine (Fig. 6). The  $\beta$ -phenylethylamine skeleton is also the backbone for the neurotransmitters dopamine, NE, and epinephrine. These neurotransmitters are synthesized from tyrosine in the nerve terminal and stored in granules and released at the nerve ending to act on postganglionic receptors (357). After acting on these receptors they can be inactivated by catechol-O-methyltransferase or taken back up into the nerve terminal.

Amphetamine ( $\alpha$ -methyl- $\beta$ -phenethylamine) is the prototype for this group of compounds. Chemical modification of the  $\beta$ -phenylethylamine structure has led to a wide range of pharmacological responses (323, 384–387). At one end of the

spectrum are derivatives that influence dopaminergic and noradrenergic neurotransmission (amphetamine). Phentermine, diethylpropion, benzphetamine, and phendimetrazine are thought to stimulate the release of NE from the nerve terminal into the interneuronal cleft, thus increasing the amount of NE interacting with postganglionic neuronal receptors (357). However, they may also stimulate dopamine release and block reuptake of NE and/or dopamine. A recent microdialysis study shows that phentermine stimulates the release of dopamine from the striatum (388). At the other end of the spectrum are drugs that affect serotonin release and reuptake such as dexfenfluramine (372). In the middle are newer drugs that block the reuptake of NE, serotonin, and dopamine (sibutramine).

*i) Phenethylamine receptors:* Paul and colleagues (389–395) explored the binding of [ $^3$ H]amphetamine and [ $^3$ H]mazindol

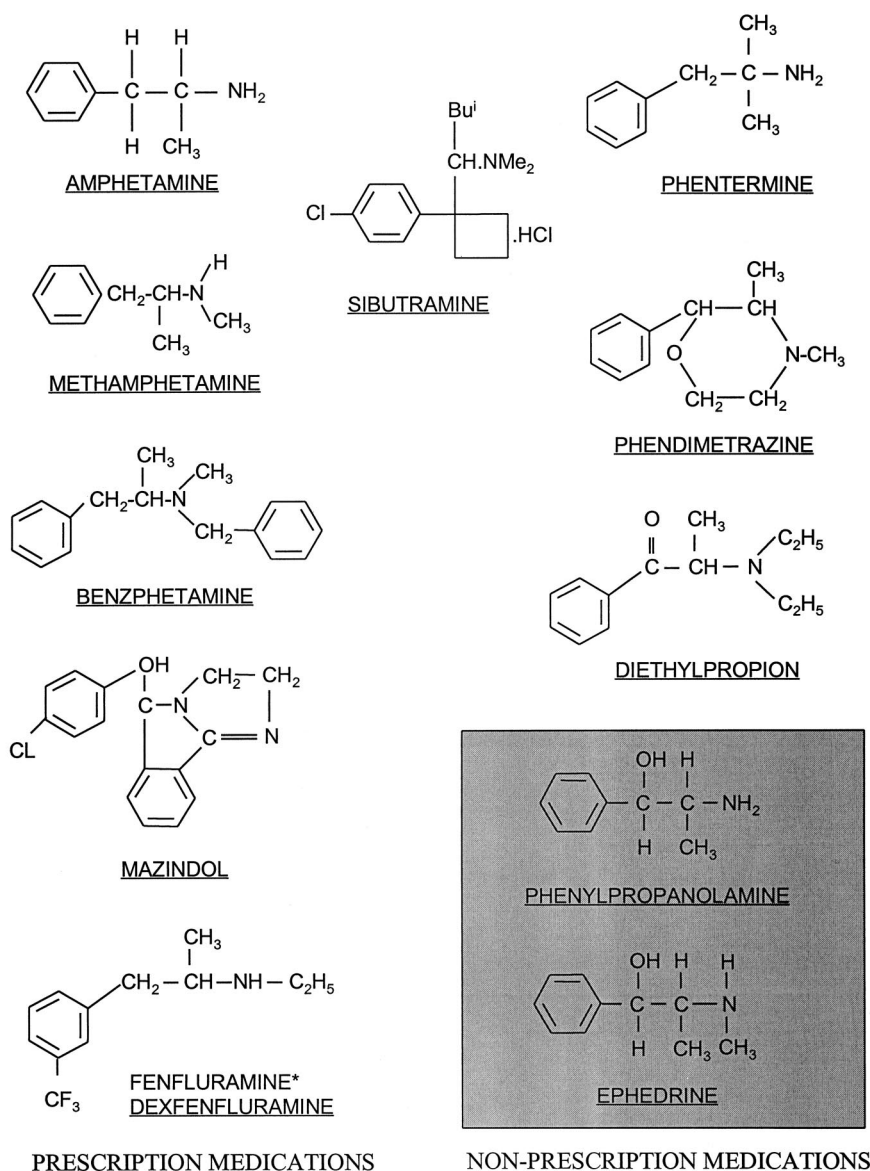


FIG. 6. Formulas for appetite suppressant drugs. Amphetamine and benzphetamine are not approved for the treatment of obesity. Fenfluramine has not been marketed since September 1997.

\*Not commercially available since 1997

to receptors in brain tissue. They demonstrated the presence of both a low- and a high-affinity saturable stereospecific protein-binding site for amphetamine and mazindol on synaptic membranes in the hypothalamus and corpus striatum (389). The relative binding affinities of the various phenylethylamine derivatives, as measured by the inhibition of [<sup>3</sup>H]amphetamine or [<sup>3</sup>H]mazindol binding, are correlated with their relative anorectic potencies but not their relative stimulant properties (Fig. 7) (392).

The amphetamine-binding sites in the hypothalamus are regulated by the levels of glucose (390, 392–395). Glucose and amphetamine seem to act at the same site in the hypothalamus to stimulate a sodium-potassium ATPase, which may be involved in the glucostatic regulation of food intake (390). Mazindol and ouabain binding are related to glucose concentration, but alloxan-induced inactivation of the glucoreceptor mechanism uncouples the anorectic drug recognition site from the hypothalamic glucostat (395). Collectively, these data suggest that ion channels involving ATP-dependent potassium channels may be involved in the mechanism of action of  $\beta$ -phenethylamine and tricyclic anorectic drugs.

*ii) Food intake:* In experimental animals all of the  $\beta$ -phenethylamine derivatives have been shown to reduce food intake, which is the primary mechanism for weight loss. In rodents the effect is dose-related and occurs rapidly after parenteral administration of the drug. In early experimental studies on dogs, Harris *et al.* (396) showed that weight loss did not occur if animals were not allowed to reduce their food intake. Garrow *et al.* (397) and Petrie *et al.* (398) showed in humans that weight loss with fenfluramine is not different than that with placebo when food intake was held constant on a metabolic unit.

The pattern of food intake differs between noradrenergic and serotonergic drugs. Amphetamine, as the prototypic drug, delays the onset of eating whereas fenfluramine does not delay the onset of eating, but hastens the termination of food ingestion (372, 399). In experimental animals, administration of serotonin (157, 213) or fenfluramine (360) reduces

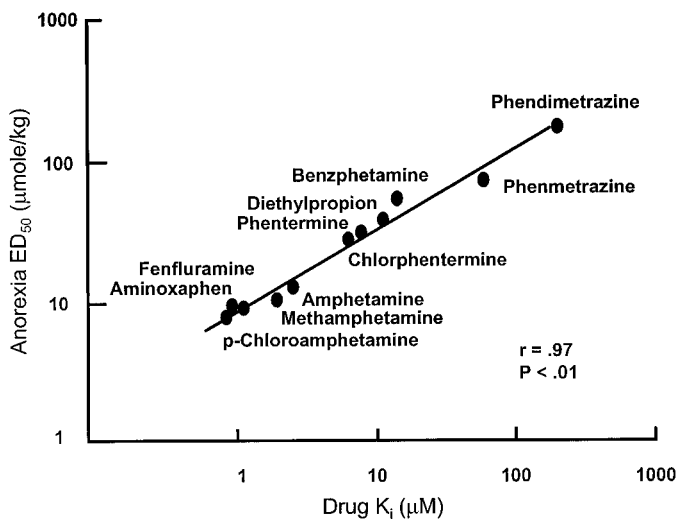


FIG. 7. Relation of appetite suppressant effect and binding to hypothalamic membranes. [Adapted with permission from I. Angel *et al.*: *J Neurochem* 48:491–497, 1987 (393). © Lippincott Williams & Wilkins]

primarily fat intake. This occurs independently of the underlying nutrient preference of the animal. Although NE injected in the PVN is claimed to increase carbohydrate intake (400), noradrenergic drugs have not been reported to have selective effects on macronutrient intake (415).

*iii) Thermogenesis:* Some of the  $\beta$ -phenethylamine drugs are thermogenic in animals. Mazindol stimulates oxygen consumption (401) and increases NE turnover in brown fat (402, 403). Although mazindol seems to be the most robust stimulator of thermogenesis in rodents, other anorectics, such as diethylpropion, have a stimulatory effect on oxygen consumption as well (401). Fenfluramine, mazindol, and amphetamine, but not diethylpropion, increase the thermogenic activity of brown adipose tissue in rats (402, 403). Dexfenfluramine produces a pattern of response in the experimental animal that has some similarities to a lesion in the lateral hypothalamus (404, 405), although not all accept this view (406). During chronic treatment with dexfenfluramine, food intake initially falls and then gradually returns to normal, although body weight remains 10–15% below control, probably as the result of activation of the sympathetic nervous system to brown adipose tissue (404). In animals that have lost weight before receiving the drug, dexfenfluramine does not reduce food intake (406). In addition, the lateral hypothalamus-lesioned animal is more sensitive to fenfluramine (407), suggesting that stimulating factors for feeding from the lateral hypothalamus (possibly orexins; see below) and the serotonin system affected by fenfluramine may both be feeding into the same CNS elements. Sibutramine, which blocks reuptake of NE, serotonin, and dopamine, reduces food intake and also stimulates thermogenesis in brown fat of experimental animals (408).

#### b. Clinical pharmacology.

*i) Pharmacokinetics:* The noradrenergic appetite suppressant drugs are generally well absorbed from the GI tract (409, 410). Peak blood levels occur within the first 1–2 h for most of them (Table 7). Removal from the blood occurs by metabolism or conjugation in the liver, which produces active metabolites from some drugs (fenfluramine, sibutramine) and inactivates others. The excretion of unmetabolized drugs and their metabolites into the urine is accelerated when the urine is acidified. The plasma half-life is long for fenfluramine, dexfenfluramine, and for the metabolites of sibutramine (411). For the other drugs it is shorter. Obesity can affect the metabolism of appetite suppressant drugs (411). Dexfenfluramine has a high clearance and large tissue distribution in both excess lipid and lean tissues (411). There is similar data for the other sympathomimetic drugs (412–414).

*ii) Food intake:* A documented reduction in food intake of human beings occurs after the administration of several of the appetite-suppressing drugs (399, 415–418, 502, 650). The noradrenergic drugs reduce food intake without specific effects on macronutrient selection (415). Effects of *d*-amphetamine on food intake are attenuated by odensatron, a 5-HT<sub>3</sub> antagonist, suggesting that a serotonin pathway may be involved in the response to noradrenergic drugs (205).

The serotonergic drugs (fenfluramine and dexfenfluramine) have been reported to reduce food intake of carbohydrate cravers (419). The design of the experiments on which



TABLE 7. Pharmacokinetic data on anorectic drugs

	Time to peak (h)	$t_{1/2}$	DEA schedule	Self- administered	Anorectic reinforcing ratio <sup>b</sup>	Dose
<i>d</i> -Amphetamine <sup>a</sup>	1–2	10–30	II	+	1.0	5–30 mg/day
Dextroamphetamine <sup>a</sup>	1–2	10–12	II	+	1.0	5–30 mg/day
Metamphetamine <sup>a</sup>	1–2	4–5	II	+	1.0	15 mg/day
Phenmetrazine	1–2	2–10	II	+	0.41	75 mg/day
Benzphetamine	1–2	6–12	III	+	NA	25–150 mg/day
Phendimetrazine	1–2	2–10	III	+	NA	70–210 mg/day
Chlorphentermine <sup>c</sup>	1–2		III	±	0.23	65 mg/day
Chlortermine <sup>c</sup>	1–2		III	±	0.19	50 mg/day
Diethylpropion	1–2	4–6	IV	+	1.22	75 mg/day
Mazindol	1–2	10	IV	+	NA	1–3 mg/day
Phentermine	4–8	19–24	IV	+	0.21	15–37.5 mg/day
Fenfluramine	2–4	11–30	IV	–	0	60–120 mg/day
Dexfenfluramine	1–8	17–20	IV	–	NA	30 mg/day
Sibutramine <sup>d</sup>	1–3	1–16	IV	–	NA	5–30 mg/day
Phenylpropanolamine	1–2	3–4	OTC	–	0	75 mg/day
Ephedrine <sup>e</sup>	1–2	3–6	OTC	±	NA	75 mg/day

NA, Not available; OTC, over the counter, no prescription; DEA, Drug Enforcement Agency.

<sup>a</sup> Drugs in Schedule II are not approved for use in obesity.

<sup>b</sup> Anorectic/reinforcing ratio: Dose of medication suppressing baboon food intake 50% (mg/kg/day). Lowest reinforcing dose in baboon (mg/kg/infusion).

<sup>c</sup> No longer marketed.

<sup>d</sup> Not yet marketed.

<sup>e</sup> Usually used in combination with caffeine for treatment of obesity.

this conclusion is based used snack foods that contained both carbohydrate and fat, making it difficult to separate macro-nutrient intake when snack intake was suppressed. Much of the other literature suggests that serotonin and dexfenfluramine reduce fat and protein intake (399, 415, 416, 418, 420) or all nutrients (650). Dexfenfluramine inhibits total food intake more than *l*-fenfluramine (417). Combining *d*-amphetamine with *d*-fenfluramine was not more effective in reducing food intake than *d*-amphetamine alone (417), but the combination did reduce intake of sweet tasting foods more than the individual compounds. Dexfenfluramine is twice as potent in reducing food intake as *d*-norfenfluramine, its active metabolite (421). Dexfenfluramine decreases meal size and nearly eliminates snacking (420). Dexfenfluramine is most effective in decreasing food intake on a high-fat diet, and studies in humans suggest that dexfenfluramine decreases food intake by a selective effect on dietary fat (422). In a double-blind placebo-controlled, latin square trial in 12 healthy men, Goodall *et al.* (423) showed that 30 mg of dexfenfluramine significantly reduced fat intake. *d*-Fenfluramine administered for 3 days also significantly reduced the intake of a test meal, more so when the preload meal was high in protein as compared with carbohydrate (424).

Ritanserlin, a putative 5-HT<sub>2C</sub> antagonist, abolished the reduction in food intake by dexfenfluramine and also abolished the rise in PRL and temperature (423). mCPP, a 5-HT<sub>2C</sub> agonist, decreased feeding in humans (425). The hypophagic, endocrine, and subjective responses to mCPP in healthy men and women suggest that 5-HT<sub>2C</sub> receptors may mediate some of the effects of serotonin on feeding (425). On the other hand, sumatriptan, a selective 5-HT<sub>1B/D</sub> receptor agonist, reduced food intake in a double-blind placebo-controlled cross-over study in 15 healthy females. The major reduction was in fat intake (426). In addition to decreasing food intake, sumatriptan also increased plasma GH in healthy women

(426). Thus, both 5-HT<sub>1B/D</sub> and 5-HT<sub>2C</sub> are still candidates for the anorectic effects of serotonin in humans.

*iii) Cardiovascular effects:* Since  $\beta$ -phenethylamine is the backbone for the available appetite-suppressing drugs as well as for dopamine, NE, and epinephrine, one might expect that the noradrenergic appetite-suppressant drugs would be sympathomimetic and affect the cardiovascular system. These noradrenergic appetite-suppressant drugs have small stimulatory effects on heart rate and blood pressure after acute administration. Relative to amphetamine set at 1 mg, phenmetrazine required 2–4 mg to produce the same effect on blood pressure and benzphetamine and diethylpropion 8–10 mg (427). Fenfluramine, in contrast to amphetamine, had essentially no effect on blood pressure, temperature, or sleep but caused reduction in food intake and a greater dysphoria in human beings than amphetamine (428). In most reports, the return to normal of pulse and blood pressure may be partly the result of weight loss that lowers blood pressure (429–434).

Blood pressure drops with weight loss in most but not all patients (435). Pulse rate also drops with weight loss but stabilizes by the third week of treatment (424, 433, 436). During treatment with most appetite suppressant drugs or with diet alone (431), blood pressure and pulse rate dropped to or below baseline by 8–12 wk (432–434). Sibutramine appears to be an exception to this rule. This drug produces a small dose-related rise in diastolic blood pressure of 3–5 mm Hg and a rise in pulse of 2–4 beats per minute (bpm) (689), which does not return to baseline even during 2.5 yr of treatment (137).

Dexfenfluramine and fenfluramine lower blood pressure in normotensive (437, 438) and hypertensive (439) obese patients. Blood pressure is also reduced in short-term studies when weight loss is prevented (440, 441). Using ambulatory blood pressure monitoring equipment, the reduction in

blood pressure during treatment with dexfenfluramine occurred during the day with no change at night (441). In a 4-day cross-over trial in which food intake was held constant, supine and standing systolic and diastolic blood pressure were decreased by dexfenfluramine (440). Plasma noradrenaline and renin were also decreased independent of weight loss during short-term treatment with dexfenfluramine (440).

*iv) Metabolic and endocrine effects:* Weight loss itself corrects many of the metabolic abnormalities associated with obesity (20, 22, 23, 442). Early studies showed that fenfluramine, independent of weight loss, acutely increased glucose disposal (443, 444) and had a hypoglycemic action in diabetes mellitus. In contrast, Petrie *et al.* (398) did not find that fenfluramine lowered blood glucose, and Larsen *et al.* (445) found the effect initially but after 7 days there was no residual effect of dexfenfluramine on an iv glucose tolerance test. In a double-blind cross-over study of 10 overweight women who received placebo and dexfenfluramine (15 mg twice daily) body weight remained constant. During the treatment period with dexfenfluramine, serum insulin, serum C-peptide, and total cholesterol were significantly reduced compared with the placebo period. Dexfenfluramine also significantly reduced glucose oxidation in the basal state and tended to increase glucose disposal during an euglycemic hyperinsulinemic clamp (446). Dexfenfluramine administered to weight-stable subjects on a metabolic ward also showed that insulin-requiring diabetics needed 21% less insulin while taking fenfluramine as compared with placebo. Dexfenfluramine treatment has been associated with a selective reduction of visceral fat during weight loss that correlates with improved insulin resistance and a reduction of hepatic fat (447, 448). Dexfenfluramine increases fatty acid turnover and oxidation while reducing serum glucose in diabetic subjects independent of weight loss (448).

Endocrine changes have been reported with some appetite suppressants. Dolecek (450) evaluated a battery of endocrine tests in subjects taking mazindol or placebo. Mazindol lowered insulin and GH during an oral glucose tolerance test but increased  $T_4$ . There were no changes in FSH, LH, testosterone, renin, angiotensin II, GH during an insulin tolerance test,  $T_3$  uptake, BMR, achilles tendon reflexes,  $T_3$  RIA, 17-ketosteroids, testing with metyrapone, or after stimulation with ACTH. Mazindol also delayed gastric emptying significantly (452). Another appetite suppressant, fenfluramine, changed ACTH patterns to a more circadian pattern while GH secretion at night diminished (451).

The serotonergic drugs fenfluramine and dexfenfluramine also affect the endocrine system. Dexfenfluramine is a more potent stimulus for PRL secretion than *l*-fenfluramine (453), and amphetamine had no significant effect. The rise in PRL produced by dexfenfluramine can be attenuated in lean women by naloxone, an opioid antagonist, but in obese women naloxone had no effect on the rise in PRL (454). In contrast, the rise in ACTH and cortisol after naloxone was significantly higher in obese than in lean women and 7 days of treatment with dexfenfluramine attenuated the response to naloxone (455). The response to CRH was similar in lean and obese women and was unaffected by dexfenfluramine. In a 7-day cross-over study, the cortisol and ACTH response to naloxone was higher in the obese than in control women

and was reduced by dexfenfluramine. In contrast, ACTH and cortisol responses to CRH were not different in obese and control women and were unaffected by dexfenfluramine (455). When healthy men were given dexfenfluramine and *d*-amphetamine, the rise in cortisol was greater than with either one alone (626).

Dexfenfluramine was also found to enhance release of the GH after administration of GH-releasing hormone (456, 582). The rise of GH after injecting GH-releasing hormone was significantly higher, and the insulin levels were lower in dexfenfluramine-treated subjects than in the placebo-treated group, probably reflecting their different central monoamine response system, but this result may have been influenced by diet (456). Kars *et al.* (457) found no effect of dexfenfluramine on galanin or GH-releasing hormone stimulation of GH release in a double-blind placebo-controlled 6-day randomized cross-over trial. Dexfenfluramine increased PRL levels in subjects with endogenous depression, obsessive-compulsive disorder, and panic disorder but less so than in normal controls (458–460). The PRL response to fenfluramine improves after depression remits (461). Fenfluramine (60 mg) increases PRL 42% and decreases cortisol 33% in depressed subjects compared with an 80% increase in PRL and a 94% increase in cortisol in the normal controls (462). The PRL response to dexfenfluramine improved with treatment of depression but the cortisol response remained blunted (462–464).

*v) Thermogenesis:* A thermogenic effect for many appetite-suppressing drugs is clear from the animal data (402, 403). Human data are less clear cut. The potential thermic response to dexfenfluramine was examined in several studies. Using a calorimeter, Breum *et al.* (465) measured energy expenditure in patients before and after 13 months of treatment with dexfenfluramine or placebo and found no differences in thermogenesis. These subjects were treated with a very-low-calorie diet and had lost weight, which may contribute to the findings. Van Gaal *et al.* (466) reported that resting metabolic rate (RMR) fell less during 3 months of treatment with dexfenfluramine (30 mg/day) and a very-low-calorie diet compared with placebo in 32 obese postmenopausal women. In an acute study using a double-blind cross-over protocol, Scalfi *et al.* (467) found that RMR in the fasting state was increased by dexfenfluramine compared with placebo. Postprandial thermogenesis was also increased in these obese males confirming the data of Levitsky *et al.* (468, 469). In contrast Lafreniere *et al.* (422) found no effect at 1 wk or 3 months in a study comparing placebo- and dexfenfluramine-treated men and women. One difference between the paper by Lafreniere *et al.* (422) and the one by Scalfi *et al.* (467) is the heterogeneity of the patients whose variance may have swamped small effects.

Sibutramine is thermogenic in animals (408) but the human data are contradictory. Seagle *et al.* (470) conducted a randomized clinical trial and measured RMR at baseline and 3 h after the first dose of sibutramine or placebo and again after 8 wk of treatment with sibutramine. They detected no difference between placebo and drug at any time point (470). Hansen *et al.* (471) conducted a double-blind latin square study in which healthy men received sibutramine or placebo either fasting or with a meal. Energy expenditure was measured over 5 h. They reported that over the last 3.5 h sib-

uramine increased energy expenditure in both the fed and fasted state (471). It is the late effect that was probably lost in the first trial. Energy expenditure is not increased by PPA (472).

c. *Clinical trials with noradrenergic weight loss drugs.* Both short-term and long-term clinical trials have established the effectiveness of noradrenergic drugs. Weight loss was significantly greater than placebo in most trials, but the magnitude of the weight loss was variable.

i) *Short-term clinical studies of 3 months duration with single drugs:* In 1976 Scoville (106) summarized studies submitted to the USFDA to support new drug applications for appetite-suppressing drugs (Table 8). There were more than 200 double-blind controlled studies in this database in which subjects were measured serially and in which the data had been submitted to the FDA. These studies involved a number of different anorectic drugs including amphetamine, methamphetamine, phenmetrazine, benzphetamine, phendimetrazine, phentermine, chlorphentermine, chlortermine, mazindol, fenfluramine, and diethylpropion. There were 4,542 subjects receiving active medication and 3,182 subjects receiving placebo. More than 90% of these studies demonstrated more weight loss on active medication. The drop out rate was about 24.3% at 4 wk and 47.9% at the end of studies that lasted from 3 to 8 wk or more. Subjects receiving active medication lost 0.23 kg/wk (0.5 pound/wk) more than placebo, were twice as likely to lose 0.45 kg/wk (1 pound/wk) as the placebo subjects (44% vs. 26%), and lost approximately twice as much weight as the placebo subjects. Administration of the appetite-suppressing drugs included in this review produced comparable weight loss. Since there was no difference in the weight loss produced by the various agents, the choice between them would seem to hinge upon their respective side effects and potential for abuse (see below).

Figure 8 uses data from one of the clinical trials submitted to the FDA (6). It was selected since it was one of the longest in this set, lasting 20 wk. All 15 patients in the control group and 30 patients in the drug-treated group completed the trial. It is clear that the patients who received biphetamine (a mixture of *d*-amphetamine and *l*-amphetamine) lost significantly more weight, and that the difference from placebo continued to widen through the entire 20-wk trial, although

TABLE 8. Summary of results on patients treated with placebo or active drug

	Placebo	Active drug
No. of patients	4,543	3,182
Drop outs		
Four weeks of treatment	18.5%	24.3%
End of study	49.0%	47.9%
Weight loss achieved		
1 lb/wk	26%	44%
3 lb/wk	1%	2%
Patients achieving a given weight loss over 4 wk		
1 lb/wk	46%	68%
3 lb/wk	4%	10%

Reprinted with permission from B. A. Scoville. In: *Obesity in Perspective*. DHEN Publication No. (NIH) 75-708, pp 441-443, 1975 (106).

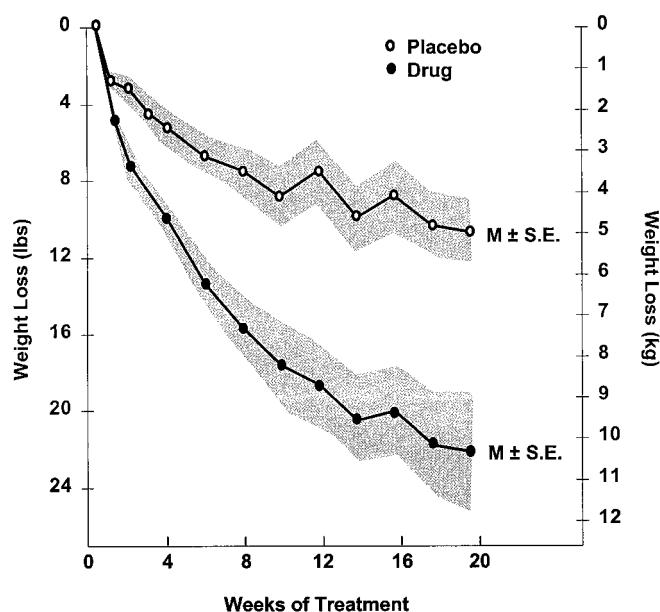


FIG. 8. Comparison of placebo and amphetamine-like drug. The drug-treated group consisted of 30 patients, and the placebo group consisted of 15 patients, all of whom completed the 20-week trial. [Adapted with permission from G. A. Bray. In: *The Obese Patient*, p. 371, 1976 (6).]

a plateau at approximately 10 kg was evident in the drug-treated patients (Fig. 8) (6).

Tables 9 and 10 list the short-term studies that met our criteria. To be selected for inclusion in this table, studies had to be published in English and had to be double-blind controlled trials lasting 8 wk or more or the first half of a crossover study lasting 16 wk or more. Only studies that included the initial body weight, number of subjects, and final weights were used. This allowed us to calculate the percentage weight loss and to evaluate "success" using the FDA-drafted criteria (112) or the European CPMP criteria. The short-term studies have been subdivided into two tables, one including noradrenergic drugs (Table 8) and the other one the serotonergic drugs fenfluramine and dexfenfluramine (Table 9). Several drugs are not available on the US market but were reviewed to see whether they had any unexpected lessons [aminorex (473-477); benfluorex (478-480); flutiorex (481); oborex (482); Ro4-5282 (483-485)]. Some studies on drugs in US Drug Enforcement Agency Schedule II (*d*-amphetamine, methamphetamine, phenmetrazine) were also reviewed. *d*-Amphetamine is the prototypic sympathomimetic appetite suppressant drug that has provided much insight into the biology and pharmacology of noradrenergic drugs as well as the problems of drug addiction. The following studies were reviewed, but not used: *d*-amphetamine (483, 486, 487); phenmetrazine (488-493); chlorphentermine (487, 489, 494).

a. *Noradrenergic drugs.* Several features of Table 9 deserve comment. First, few studies met either the proposed FDA or CPMP criteria, even though in 3-month (12-wk) studies 75% or so of the maximal weight loss would be achieved. Two drugs, mazindol and phentermine, had a number of trials meeting these criteria. It is also noteworthy that neither criterion was clearly superior.

TABLE 9. Short-term studies with noradrenergic drugs

Author	Year	No. subjects		Dose (mg/day)	Duration of study (wk)	Initial wt (kg)		Wt loss (kg)		Wt loss (%)		Met criteria		Comments
		Start P/D	Complete P/D			Placebo	Drug	Placebo	Drug	Placebo	Drug	FDA	CPMP	
<b>Diethylpropion</b>														
Andelman <i>et al.</i> (495)	1967	46/51	10/37	75	11	82.2	84.7	+0.3	-5.1	+0.3%	-5.1%	Yes	Yes	Adolescents
Bolding (496)	1968	25/27	18/17	75	12	78.0	85.8	-4.9	-8.1	-6.3%	-9.4%	No	No	Women
Boileau (497)	1968	53/53	52/53	75	13	67.1	70.5	+3.2	+0.5	+4.8%	+0.7%	No	No	Pregnant
Bolding (498)	1974	25/25	20/21	75	12	87.0	81.2	-4.5	-6.6	-5.0%	-8.3%	No	No	Women
McQuarrie (499)	1975	19/22	18/22	75	12	74.4	84.3	-1.5	-4.4	-2.1%	-5.5%	No	No	4-wk run-in, intermittent drug group
Abramson <i>et al.</i> (120)	1980	40/40	28/32	75	12	82.5	80.3	-3.7	-6.6	-4.4%	-8.0%	No	No	With behavior therapy
Mazindol														
Hadler (519)	1972	20/40	19/27	2	12	107.6	93.7	-4.4	-5.4	-4.1%	-5.8%	No	No	Skinfold decreased more with mazindol; wt loss not different
Kornhaber (520)	1973	15/15	12/14	3	12	73.3	74.9	-2.4	-8.5	-3.3%	-11.3%	Yes	Yes	Compared to <i>d</i> -amphetamine
Sharma <i>et al.</i> (523)	1973	58/58	43/50	2	12	77.6	78.6	-5.4	-8.6	-7.0%	-10.9%	No	Yes	Children (11-18 yr)
Vernace (522)	1974	33/32	30/30	2	12	83.3	83.9	-2.5	-6.4	-3.0%	-7.7%	No	No	Compared to <i>d</i> -amphetamine
Bauta (524)	1974	20/20	11/12	2	12	79.4	78.9	-3.8	-13.8	-2.2%	-8.0%	Yes	No	Adolescents (12-18 yr)
Crommelin (525)	1974	20/20	18/18	1	12	82.1	87.9	-2.5	-4.5	-3.0%	-5.1%	No	No	Diabetics
Elmaleh and Miller (526)	1974	20/40	17/33	2	12	80.7	79.8	-0.4	-2.2	-0.5%	-2.7%	No	No	Wt $\Delta$ significant $P < 0.01$
Heber (527)	1975	25/25	20/20	2	12	77.5	84.6	-1.6	-6.9	-2.1%	-8.1%	Yes	No	Difference significant $P < 0.001$
Sedgwick (528)	1975	30/30	24/27	2	12	84.8	82.0	-6.6	-8.4	-7.7%	-10.3%	No	No	Significant $\downarrow$ in cholesterol
Woodhouse <i>et al.</i> (529)	1975	9/12	7/11	3	12	82.6	76.4	-0.5	-0.5	-0.6%	-6.5%	Yes	No	$\Delta$ wt $P < 0.001$
MacLay and Wallace (530)	1977	207/207	137/155	2	12	83.0	80.8	-4.6	-7.2	-5.5%	-8.9%	No	No	Diabetics
Slama <i>et al.</i> (531)	1978	24/22	18/19	2	12	81.0	84.9	-4.2	-13.5	-5.2%	-15.9%	Yes	Yes	$\Delta$ wt significant $P < 0.01$
Yoshida <i>et al.</i> (532)	1994	18/18	14/18	1.5	12	97.8	97.8	-4.5	-13.5	-4.6%	-13.8%	Yes	Yes	$\Delta$ wt $P < 0.01$
Phendimetrazine														
Hadler (548)	1968	42/45	35/36	105	12	92.1	96.7	-0.5	-3.4	-0.5%	-7.5%	No	No	$\Delta$ wt $P < 0.01$
Phentermine														
Cohen <i>et al.</i> (549)	1968	40/40/40	37/39/39	20	12	81.8	88.2	-4.0	-2.6	-8.9%	-2.9%	Yes	Yes	Prisoners phentermine compound = (20 mg phentermine + 5 mg <i>d,l</i> -amphetamine, 5 mg <i>d</i> -amphetamine)
				10	Females	85.5	90.9	-9.5	-6.0	-11.1%	-6.6%	No	No	
					Males									

P/D, Placebo/drug.

TABLE 10. Short-term studies with the serotonergic drugs dexfenfluramine and fenfluramine

Author	Year	No. subjects		Dose (mg/day)	Duration of study (wk)	Initial wt (kg)		Wt loss (kg)		Wt loss (%)		Met criteria		Comments
		Start (P/D)	Complete (P/D)			Placebo	Drug	Placebo	Drug	Placebo	Drug	FDA	CPMP	
<b>Dexfenfluramine</b>														
Finer <i>et al.</i> (123)	1985		24/26	30	12	81.9	81.7	-1.4	-5.3	-1.7	-6.5	No	No	General practice Hospital
			20/19			86.6	91.5	+1.7	-2.8					
Enzi <i>et al.</i> (437)	1988	69/64	68/59	60	12	87.2	84.0	-3.5	-8.1	-4.0	-9.6	Yes	No	
					(90 day)									
Goodall <i>et al.</i> (577)	1988	16/17	7/9	30	12	92.4	91.9	-2.8	-5.4	-3.0	-5.8	No	No	Schizophrenic on neuroleptic medications
Kolanowski <i>et al.</i> (439)	1991	14/16		30	12	101.0	95.4	-1.4	-6.0	-1.3	-6.3	Yes	No	Borderline hypertension
Willey <i>et al.</i> (578)	1992	24/25	23/22	30	12	87.7	98.7	-0.6	-3.8	-0.7	-3.9	No	No	Diabetics on oral agents
Lafreniere <i>et al.</i> (422)	1993	15/15	15/15	30	12	91.9	93.2	+0.4	-4.6	-0.4	-4.9	No	No	Measured TEF too
Stewart <i>et al.</i> (579)	1993	20/20	18/20	30	12	101.5	94.3	+0.4	-3.7	-0.4	-3.9	No	No	Diabetic diet and/or sulfonylurea; 4-wk run-in
Bremer <i>et al.</i> (580)	1994	14/15	14/12	30	12	86.8	79.3	+0.4	-2.1	-0.5	-2.6	No	No	Dyslipidemia 8-wk run-in
Willey <i>et al.</i> (581)	1994	11/9	11/9	30	12	86.6	94.7	-2.0	-1.1	-2.3	-1.1	No	No	Diabetics insulin and metformin
Drent <i>et al.</i> (582)	1995	58/54	52/51	30	9	93.6	93.7	+0.2	-3.1	+0.2	-3.3	No	No	↓ fat and CHO intake
Van Gaal <i>et al.</i> (466)	1995	15/11		30	12	94.5	96.6	-12.8	-16.0	-13.5	-16.5	No	No	VLCD Dexfen pre-vented drop in RMR
Swinburn <i>et al.</i> (583)	1996	42/42	39/38	30	12	95.5	93.1	-0.3	-4.2	-0.3	-4.4	No	No	12-wk run-in low-fat diet
Galletly <i>et al.</i> (584)	1996	11/10	16	not given	12	100.3		-3.3	-3.2	-3.3	-3.2	No	No	Half of a 24-wk cross-over trial
<b>Fenfluramine</b>														
Munro <i>et al.</i> (600)	1966	30/30	25/25	80	12	89.0	90.9	+0.2	-4.2	+0.2	-4.6	No	No	Slow release, 2-wk run-in 8 wk rx
Weintraub <i>et al.</i> (601)	1983	25/26	19/18	60	8	85.3	88.7	-3.3	-5.9	-5.5	-8.0	No	No	Dyslipidemics
Brun <i>et al.</i> (602)	1988	22/22	22/18	60	12	85.6	85	-0.0	-3.0	0	-3.5	No	No	

P/D, Placebo/drug; VCLD, very-low calorie diet; CHO, TEF

All groups treated with sympathomimetic drugs (Table 9) lost weight except the study of pregnant women (497). This ranged from a low of 2.1 kg to a high of 16.0. In all but two studies (495, 497) the placebo-treated patients lost weight. In the review by Scoville (106), the mean effect size for rate of weight loss (difference between drug effect and placebo effect) was 0.25 kg/wk.

Intermittent therapy has been reported with several drugs (131, 499, 501, 506, 519–521, 558, 576). Only one of these trials lasted more than 12 wk (131). Four of the trials showed no difference in weight loss between the fenfluramine-*d*-amphetamine (575), mazindol-*d*-amphetamine (521), diethyl propion-mazindol (505), or mazindol-fenfluramine (520), but a small trial comparing mazindol and *d*-amphetamine (519) favored mazindol.

Several multicenter trials have been reported (124, 521, 530, 535, 538, 541, 624). Three multicenter trials in general practice (521, 530, 538) provide information on real world uses of appetite suppressants over a short time period. One group of investigators compiled data on several agents administered over 12 wk to patients defined as having "refractory" obesity or the inability to lose weight on a prescribed diet (55) (Fig. 9). The weight losses were modest, only 1–4 kg, and three of the six drugs (diethylpropion, mazindol, and chlorphentermine) were almost identical.

Many different patient groups have been tested with these drugs. They include children who were treated with diethylpropion (495, 504, 509), mazindol (523, 524), and phentermine (556). The responses were in general similar to those of adults. These drugs have also been used in patients with hypertension (503, 543) and with cardiovascular disease (507, 508) without reported ill effects.

Since appetite suppressants do not cure obesity, one would expect an effective drug to lower body weight and to have weight gradually return to control when the drug was stopped. Although we have not included the cross-over data in our analysis it is instructive in many instances in showing weight regain or slower weight loss after the medication is changed to placebo. One example from an open-label study is shown in (Fig. 10). At the beginning of this study of 21 patients, weight loss occurred with diet and expectations of weight loss but no medication. On subsequent occasions when placebo or no medication was given, subjects gained weight. When receiving drugs, patients lost weight. This response to discontinuing an effective drug, *i.e.*, weight regain, is the expected result from withdrawing an effective therapeutic agent.

Comparative data using two active agents with or without placebo have been reported for most of the drugs (110, 489, 501, 503, 506, 518, 537, 539, 542, 544, 555, 558). As noted by Scoville (106) there was no consistent value of one drug over the other.

Plasma concentrations have been used to test predictability of weight loss (554, 634). The initial data were promising, but two other studies failed to find that plasma levels were predictive of success. However, in the International Dexfenfluramine (INDEX) trial of fenfluramine, Guy-Grand (652, 653) reported a good relationship between plasma fenfluramine and weight loss. Patients believed to be taking drugs

but who had none in their serum lost only as much weight as the placebo-treated patients.

PPA is an  $\alpha_1$ -adrenergic agonist of the propranolamine group. It is an over-the-counter preparation with a provisional FDA approval for weight loss. The three published double-blind controlled clinical trials of PPA lasting 8 wk or more are included in Table 9. In a review by Weintraub (573) and Greenway (567), including published and unpublished studies obtained from the manufacturer, 1,439 subjects received active medication and 1,086 received placebo (567, 573). At the end of the studies, which were up to 12 wk in length and performed before 1985, PPA-treated subjects lost about 0.27 kg/wk more than subjects receiving placebo. This was similar to the results reported by Scoville (106). In the studies performed after 1985, the rate of weight loss over 4 wk was 0.21 kg/wk more than in the placebo-treated subjects. The rate of weight loss slowed after the first 4 wk, and at the end of the studies PPA-treated subjects had lost only 0.14 kg/wk more than those receiving placebo. This is consistent with the small number of studies that have directly compared PPA with prescription anorectic medication. Although there was no statistically significant difference between PPA and mazindol, or between dextroamphetamine and diethylpropion in studies lasting 4–8 wk, the mean weight loss for the prescription anorectics was 0.86 kg/wk in 123 subjects compared with 0.64 kg/wk for 121 subjects on PPA (563).

There is only one controlled trial of PPA that lasted 20 wk. In this double-blind placebo-controlled trial, 101 subjects were treated with placebo or PPA for 6 wk with an optional double-blind extension to week 20 (117). At 6 wk the PPA-treated group had lost 2.4 kg (0.43 kg/wk) compared with 1.1 kg (0.18 kg/wk) in the placebo group. In the optional extension, 24 subjects on PPA lost 5.1 kg (6.5%) compared with 12 subjects treated with placebo who lost 0.4 kg/wk (0.5%) of initial body weight ( $P < 0.05$ ).

In a study comparing 1) PPA 75 mg/day alone, 2) benzocaine gum 96 mg/day alone, and 3) the combination of PPA 75 mg/day and benzocaine gum 96 mg/day against placebo in 40 obese women over 8 wk, the PPA-treated group lost twice as much weight as the placebo-treated group (567). The group receiving the benzocaine lost essentially no weight, and the difference in weight loss between benzocaine and PPA was significant in favor of PPA. Weight loss in the group receiving combined PPA and benzocaine was equal to that of the placebo group.

*b. Serotonergic drugs.* The short-term studies with dexfenfluramine and fenfluramine are presented in Table 10. In this group of studies, two using dexfenfluramine (439, 574) met the FDA criteria, but none met the CPMP criteria. However, these studies were all 12 wk or less. Weight losses in the drug-treated patients ranged from -2.6 kg (-3.3%) to -16.0 kg (-16.5%). One study was done in borderline hypertensives (439), two in diabetics (578, 579, 581), and two in dyslipidemics (580, 583).

*ii) Clinical studies of 14 or more weeks:*

*a. Noradrenergic drugs.* The longer-term double-blind placebo-controlled studies with sympathomimetic appetite sup-

pressants are summarized in Table 11. For the purpose of this table, long term is defined as trials of more than 14 wk. Included in this table are studies with diethylpropion and phentermine. Long-term studies with other noradrenergic drugs have not been published. The criteria for inclusion in this table were the same as for short-term studies.

i) *Diethylpropion*: There are two long-term placebo-con-

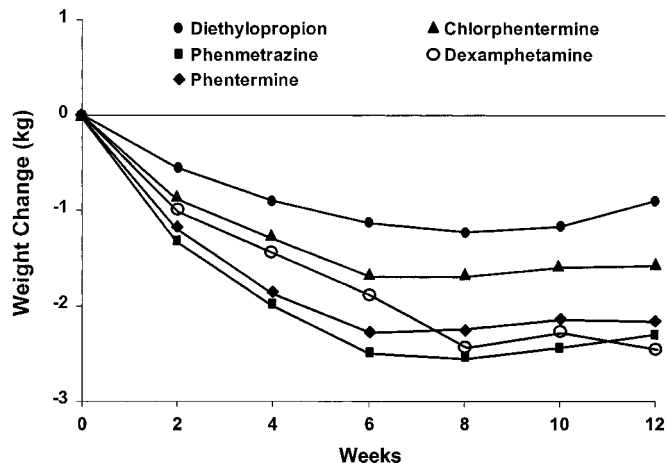


FIG. 9. Mean weight losses in refractory obesity with various anorectic agents. [Adapted with permission from J. F. Munro. In: *The Treatment of Obesity*, p. 106, 1979 (55) with kind permission from Kluwer Academic Publishers.]

trolled studies evaluating diethylpropion for weight loss (118, 641), one of which meets FDA and CPMP criteria for success and a trial comparing continuous and intermittent use of diethylpropion (576). Silverstone and Solomon (641) compared diethylpropion 75 mg/day every other month against placebo over a 1-yr period in 32 subjects. The five diethylpropion-treated subjects who completed the study lost 11% of their body weight compared with a slightly but not significantly greater 13.3% for the six subjects receiving placebo. The small number of subjects completing the trial reflect a high drop-out rate in patients who were probably not losing weight and make it difficult to interpret the study. In the other study, McKay (118) compared diethylpropion 75 mg/day to placebo treatment in a 6-month trial including 20 subjects. The diethylpropion-treated group lost 12.3% of their initial body weight compared with 2.8% in the placebo group. Blood pressure was reduced in proportion to the amount of weight lost. When diethylpropion was used continuously *vs.* every other month for 24 wk, those receiving continuous therapy lost a larger percentage of their goal weight. However, 82% dropped out in this trial, making it difficult to interpret (576).

ii) *Mazindol*: There are no long-term double-blind placebo-controlled parallel arm studies with mazindol, but there are two open-label studies that deserve comment. Enzi *et al.* (644) studied 102 patients receiving mazindol 2 mg/day and 102 patients on placebo in a 15-wk trial using a cross-over design

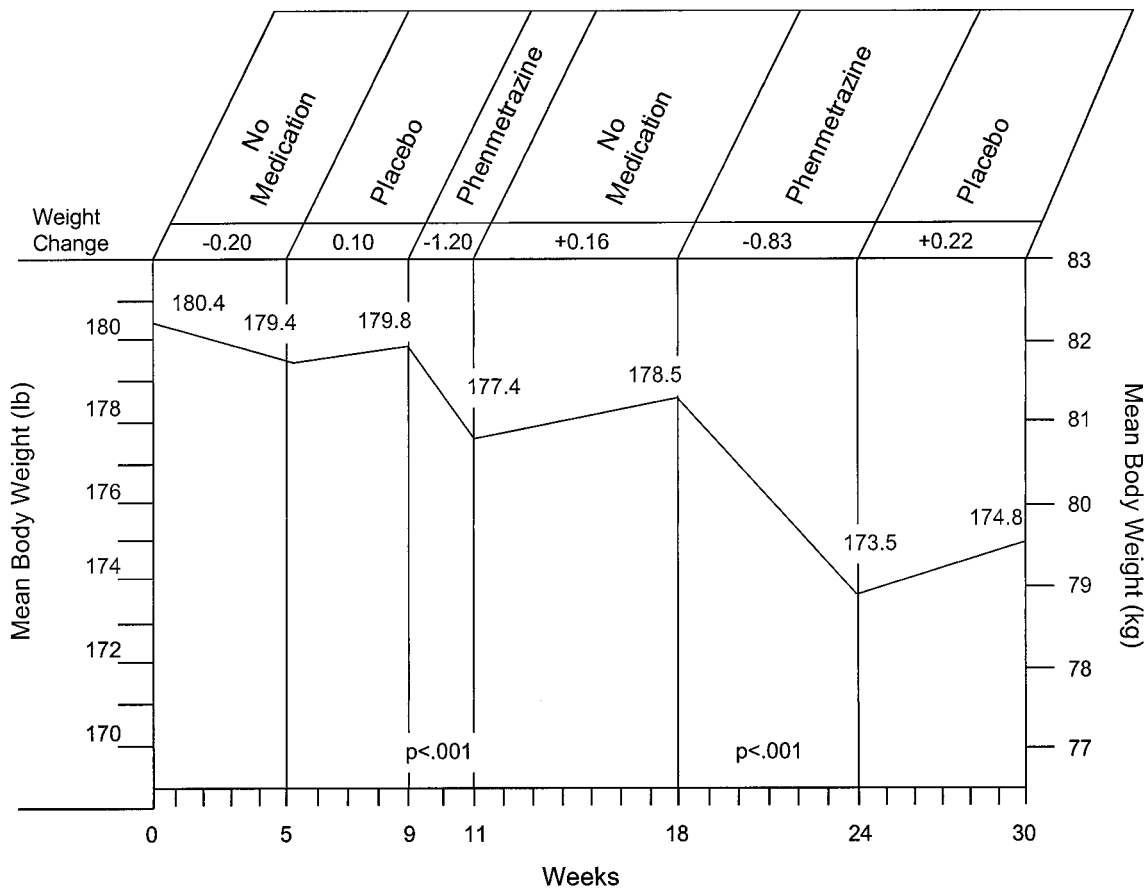


FIG. 10. Weight change with intermittent use of placebo and phenmetrazine. [Adapted with permission from J. R. Huston: *Ohio State Med J* 62:805-807, 1966 (492).]

TABLE 11. Long-term studies with noradrenergic drugs

Author	Year	No. subjects		Dose (mg/day)	Duration of study (wk)	Initial wt (kg)		Wt loss (kg)		Wt loss (%)		Met criteria		Comments
		Start (P/D)	Complete (P/D)			Placebo	Drug	Placebo	Drug	Placebo	Drug	FDA	CPMP	
Diethylpropion														
Silverstone and Solomon (641)	1965	16/16	6/5	75	52	78.8	80.7	-10.5	-8.9	-13.3%	-11.0%	No	No	Medication given on alternate months
McKay (118)	1973	10/10	6/10	75	24	84.5	92.3	-2.5	-11.7	-2.8%	-12.3%	Yes	Yes	
Phentermine														
Munro <i>et al.</i> (131)	1968	36/36 (36)	25/17 (22)	30	36	63	60	-4.8	-12.3	-7.6%	-20.5%	Yes	Yes	Intermittent Rx group lost like continuous rx
Langlois <i>et al.</i> (642)	1974	29/30	23/26	30	14	85.1	84.8	-1.7	-7.4	-2.0%	-8.7%	Yes	No	
Williams and Foulsham (643)	1981	15/15	11/11	30	24	73.6	73.6	-4.5	-6.3	-9.2%	-12.6%	No	Yes	Osteoarthritis

P/D, Placebo/drug; rx, medication.

with an additional 12 months of treatment with mazindol. There was no significant difference between the drug and placebo conditions during the 15-wk trial, but mazindol resulted in significantly more weight loss during the long-term 15-month period of treatment. Of the 49 subjects who started the 12-month extension study, 10 subjects on diet alone were compared with 11 subjects who had a total of 15 months on mazindol. Since initial weights were not given, the percentage of initial body weight lost could not be calculated.

In a 12-month open-label study of mazindol in Japan, Inoue (645) enrolled 32 subjects, half of whom dropped out before 1 yr of treatment. Using last-observation-carried-forward analysis, there was a 9% loss of initial body weight, which is comparable to drug-induced weight loss in many placebo-controlled trials with other drugs. Blood pressure, glucose, insulin, cholesterol, triglycerides, and GPT (ALT) levels declined during treatment. In a second study Inoue treated 10 patients for 8 wk with a very-low-calorie diet on an outpatient basis, another 10 with the same very-low-calorie diet on an inpatient basis, and a final 10 with a very-low-calorie outpatient diet supplemented with mazindol (645). The weight loss of the outpatients was slower than that of the inpatients, illustrating the issues of noncompliance. The outpatient group on mazindol had significantly more weight loss than those on the very-low-calorie diet alone and approached the success of the inpatient group. These three groups were followed for 1 yr using an open-label design in which 50% of the group on mazindol maintained their weight loss compared with 20% in the groups that were not given medication.

iii) *Phentermine*: There are three long-term studies using phentermine (131, 642, 643). In the first study (131), one group of patients received placebo, the second group received phentermine resin 30 mg/day, and the third group were treated with phentermine resin alternating with placebo at 1-month intervals (Fig. 11) (131). The two groups given intermittent or continuous phentermine each lost an average of 20.5% of initial body weight compared with a 6% loss of initial body weight with placebo. The group treated intermittently illustrates again the change in rate of weight loss when transferring from active drug to placebo (see Fig. 11). At each transition, weight loss accelerated or slowed

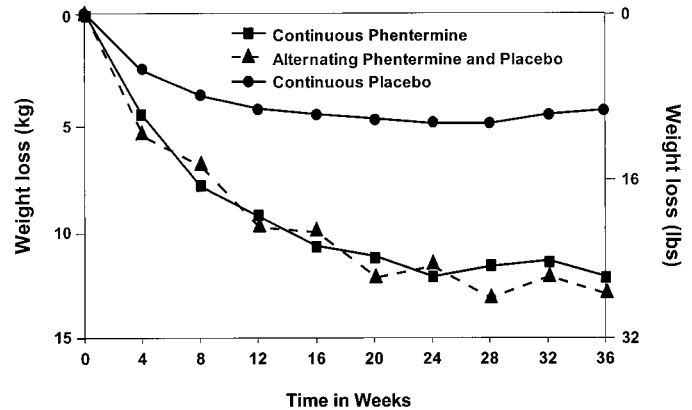


FIG. 11. Comparison of intermittent and continuous phentermine with placebo in patients with refractory obesity. [Adapted with permission from J. F. Munro *et al.*: *Br Med J* 1:352-356, 1968 (131) with permission of the BMJ.]



relative to the continuously treated patients. These authors concluded that intermittent phentermine was preferable because it was cheaper, gave equivalent weight loss, and reduced exposure to medication. In the second study (643), 30 osteoarthritic subjects were treated for 6 months with phentermine resin 30 mg/day or placebo. In the paper, the authors reported that the group treated with phentermine lost 12.6% of their body weight, compared with 9.2% for the group receiving placebo. In the third study (642), 59 subjects were treated for 14 wk with phentermine 30 mg/day or placebo. Subjects in the phentermine group lost 8.7% of their body weight compared with 2.0% for placebo.

*b. Serotonergic drugs.* Most of the data on serotonergic drugs have been collected using fenfluramine or dexfenfluramine, two drugs that block serotonin reuptake and stimulate its release. The INDEX trial was the first year-long multicenter trial of any appetite-suppressing drug. In this trial, weight loss in the drug-treated group was significantly greater than with placebo, although the placebo lost 7.5% below the baseline compared with more than 9% for the drug-treated group. The studies with fluoxetine and sertraline, selective serotonin reuptake inhibitors (SSRIs), show a modest effect on weight loss. With fluoxetine, weight is regained even while therapy is continued.

*i) Dexfenfluramine:* The largest number of long-term double-blind placebo-controlled trials have been done with dexfenfluramine and are summarized in Table 12. The criteria for inclusion in Table 12 are similar to those in Tables 8, 9, and 10, double-blind randomized controlled trials containing initial and final weights. Trials not meeting these criteria, such as trials that gave weight loss without publishing the initial weights, were not included. In the randomized, placebo-controlled multicenter INDEX trial reported by Guy-Grand *et al.* (129), 404 subjects were randomized to the placebo group and 418 received 15 mg of dexfenfluramine twice daily for 1 yr with a 2-month post-treatment follow-up. Diet decisions were left to individual centers. More subjects dropped from the placebo group for ineffectiveness (36%) than defaulted from the dexfenfluramine group for adverse events (27%). The dexfenfluramine-treated group lost 10% of initial body weight compared with 7% in the placebo group, which was statistically significant based on subjects completing the study. The percentage of subjects completing the trial and losing more than 5%, 10%, and 15% of their initial weight in the dexfenfluramine and placebo groups, respectively, was 72% *vs.* 50%, 53% *vs.* 30%, and 29% *vs.* 16% (Fig. 12).

When these percentages were recalculated on the basis of all subjects entering the trial, the percentages were approximately one quarter to one third less, but the dexfenfluramine group maintained an efficacy ratio of about 2:1 relative to the placebo group.

The results of weight loss in the INDEX trial were reanalyzed by Sandage *et al.* (593) and published in the package insert during the time the drug was marketed in the United States. This reanalysis revealed that of subjects who lost more than 1.8 kg (4 pounds) in the first 4 wk of treatment, 60% went on to lose more than 10% of their initial body weight after 1 yr of treatment, an amount that should result in health ben-

TABLE 12. Long-term studies with dexfenfluramine

Author	Year	No. subjects		Dose (mg/day)	Duration of study (wk)	Initial wt (kg)		Wt loss (kg)		Wt loss (%)		Met criteria		Comments
		Start (P/D)	Complete (P/D)			Placebo	Drug	Placebo	Drug	Placebo	Drug	FDA	CPMP	
Guy-Grand <i>et al.</i> (129)	1989	418/404	229/254	30	52	98	96.6	-7.15	-9.82	-7.3	-10.0	No	Yes	INDEX trial
Noble (438)	1990	30/30	23/19	30	24	100.8	90.0	-1.8	-6.2	-1.8	-6.9	Yes	No	INDEX substudy
Andersen <i>et al.</i> (133)	1992	21/21	13/17	30	52	106.6	92.5	-9	-10	-8.4	-10.8	No	No	INDEX substudy with VLCD
Finer (646)	1992	22/23	16/16	30	26	107.3	107.9	+2.9	-5.8	-2.7	-5.3	No	No	Wt maintenance study after wt. loss on VLCD
Mathus-Vliegen <i>et al.</i> (132)	1992	39/36	36/29	30	52	110.3	111.2	-8.0	-10.7	-7.3	-9.6	No	No	Parallel to INDEX study
Mathus-Vliegen (647)	1993	21/21	17/18	30	52	111.9	107.8	-8.6	-12.8	-7.8	-11.9	No	No	INDEX substudy
Tauber-Lassen <i>et al.</i> (648)	1990	20/20	17/15	30	52	94.9	98.6	-2.7	-5.7	-2.9	-6.3	No	No	Diabetics probably INDEX substudy
Pfohl <i>et al.</i> (649)	1994	24/24	15/19	30	52	88	94	-9.6	-10.9	-9.1	-11.2	No	No	INDEX substudy
Ditschuneit <i>et al.</i> (651)	1996	12/13	12/13	30	52	96.9	95.1	-2.8	-13.5	-2.9	-14.2	Yes	Yes	INDEX substudy
O'Connor <i>et al.</i> (656)	1995	30/30	24/27	30	24	100	93.6	-4.9	-9.7	-4.9	-10.4	Yes	Yes	1,000-12,000 kcal/day

VLCD, Very-low calorie diet.

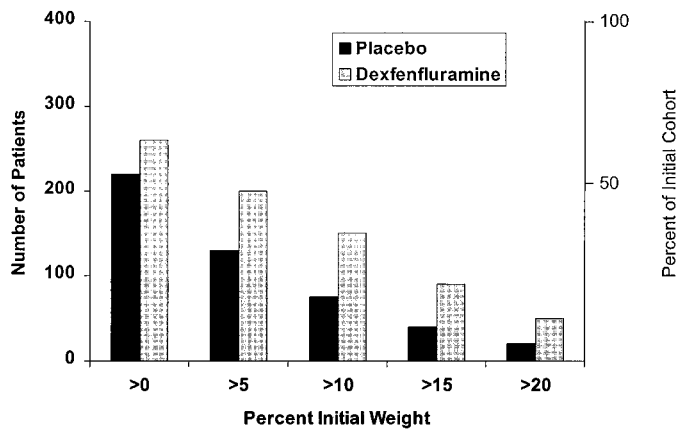


FIG. 12. Responder analysis for dexfenfluramine. These data from the International Dexfenfluramine (INDEX) trial show the percentage of patients treated with placebo or active drug who lost more than various levels of initial body weight. [Adapted with permission from B. Guy-Grand *et al.*: *Lancet* 2:1142–1144, 1989 (129). © The Lancet Ltd.]

efits. Subjects who lost less than 1.8 kg (4 pounds) in the first 4 wk of treatment lost a mean of 2.7 kg at 1 yr of treatment and only 9% lost more than 10% of body weight.

Seven of the trials in Table 12 (132, 133, 647–651) and one not included in the table (418) are substudies in the INDEX trial (129). Andersen *et al.* (133) followed 42 obese women who were treated with a very-low-calorie diet and either dexfenfluramine or placebo for 1 yr as part of the INDEX trial. These same patients appear to have been used by Breum *et al.* (465, 650). Of this group, 71% completed the trial, and there was no significant difference in weight loss between placebo- and drug-treated groups: both groups lost about 10% of initial body weight. In most of these trials except the one by Finer (646), the drug-treated patients lost 6.9–11.9% of their initial body weight, compared with 1.8–10.0% for the placebo-treated groups. Breum *et al.* reported two substudies from the INDEX trial. In one study (465), 10 obese females were used to examine energy expenditure. The 10 subjects in the dexfenfluramine group lost 16.4% of their initial body weight in comparison to the placebo group that lost 8.8% of their initial body weight. The other study (650) reported that neither food selection nor amino acids were predictors of weight loss.

One report followed up some of the participants of one site in the INDEX trial for up to 3 yr (647). At the end of the drug-treatment period, there was some initial weight regain. With the relatively small numbers of patients, the authors were able to show that weight loss was better maintained in the drug-treated patients than in those on placebo.

Mathus-Vliegen and Res (418) reported on 42 obese subjects from one site in the INDEX trial. Seven subjects dropped out. At the end of 1 yr of treatment with dexfenfluramine, the drug-treated group had lost 11.9% of their initial body weight compared with 7.8% of initial body weight in the placebo-treated group. Due to the small numbers this difference was not significant. Fifty-three percent of the dexfenfluramine group, however, lost more than 10% of their initial body weight, which was significantly greater than the 28% for the placebo group.

Noble (438) studied 60 obese subjects that had lost more than 4.5 kg but were unable to lose further. He enrolled them into a 6-month double-blind, randomized, controlled study of dexfenfluramine (30 mg/day) or placebo. Weight loss at 6 months in the dexfenfluramine group was 7% of initial body weight compared with 2% of initial body weight in the placebo group.

O'Connor *et al.* (656) reported a 6-month, double-blind study of 58 subjects randomized to dexfenfluramine (15 mg twice daily) or placebo. The dexfenfluramine group lost 10% of their initial body weight compared with 5% of initial body weight in the placebo group. Not only was there a significantly greater weight loss in the dexfenfluramine-treated group but the dexfenfluramine-treated group also had a significant improvement in lipid and insulin profile in comparison to the control group. Fifty percent of the dexfenfluramine group lost 10% or more of their initial body weight, which was significantly more than the 14.3% for the placebo-treated group.

Weight loss in patients treated with dexfenfluramine occurs over a period of 3–6 months and then remains stable during the remainder of the 1 to 1.5 yr over which it has been tested. Weight regain at the end of studies with dexfenfluramine is generally faster in those who lost most weight, which suggests that the drug remained effective until discontinued. The addition of dexfenfluramine to regimens of metformin or metformin with sulfonylureas in obese Type II diabetics using a double-blind design caused greater weight loss, better diabetic control, and lower blood pressure than in the placebo group (623).

*ii) Fenfluramine:* There are five long-term studies with *d,l*-fenfluramine worthy of discussion, but none met the criteria for inclusion into Table 12. Steel *et al.* (558) in a study lacking a placebo control group, divided 175 obese women into five groups of 35 women for a 9-month trial. This included 1) continuous fenfluramine (60 mg/day); 2) intermittent fenfluramine; 3) alternating fenfluramine and phentermine every other month (30 mg/day); 4) intermittent fenfluramine alternating with intermittent phentermine; and 5) intermittent phentermine. The group treated continuously with fenfluramine lost 13.7% of initial body weight, which was not significantly different from the intermittent phentermine-treatment group who lost 12.8% of initial body weight. The groups that had intermittent periods on fenfluramine had a higher incidence of side effects, especially depression. The authors concluded that intermittent phentermine was equally as effective as continuous fenfluramine, and that fenfluramine should not be used intermittently due to an increased risk of depression. Weintraub and colleagues (128, 699) also concluded that intermittent therapy with fenfluramine and phentermine had more side effects than continuous therapy.

Two open-label studies are particularly instructive. In one of these, Hudson (658) treated 176 subjects for 1 yr followed by a second year with no drug treatment. His three treatment groups during the first year were 1) normotensive subjects treated with *d,l*-fenfluramine (80–120 mg/day); 2) hypertensive subjects treated with *d,l*-fenfluramine; and 3) normotensive and hypertensive subjects treated with diet. The maximum reduction of blood pressure was seen in the first 4 wk

of the study and the drop was greatest in the hypertensive group receiving fenfluramine and least in the hypertensive and normotensive subjects on diet. The group treated with fenfluramine lost 10% of initial body weight over the first 6 months and maintained it for the remainder of the year, while the placebo group lost 6% of initial body weight. Over the year of follow-up after cessation of medication, subjects regained almost all of the weight they had lost, showing that this drug was effective when used, but that it did not cure obesity and did not leave any "residual" effects, thus allowing subjects to regain the weight they had lost.

In the second open-label study (659), 120 women were divided into three groups for 6 months of treatment and 6 months of follow-up. The treatment groups were 1) behavior modification; 2) fenfluramine (120 mg/day); and 3) behavior modification plus fenfluramine and an observation group. The groups receiving fenfluramine lost about 15% of initial body weight at 6 months compared with 12% treated with behavior modification alone. At 6 months of follow-up, the groups receiving fenfluramine were 6% below baseline while the behavior modification group was 10% below baseline. These differences were significant ( $P < 0.05$ ) and the authors concluded that fenfluramine gave greater weight loss but that weight was more easily regained after the medication was stopped than with behavior modification alone, probably because the "treatment effects" of behavior modification were continuing.

The only trial with *d,l*-fenfluramine that failed to show an effect of drug was an open-label study that lasted 9 months and randomized 156 patients into one of four groups who received *d,l*-fenfluramine 60 mg/day; *d,l*-fenfluramine 40 mg/day; *d,l*-fenfluramine 20 mg/day; or placebo and diet. The groups lost between 4% and 11% of initial body weight, but there was no significant difference between groups (660).

### iii) Fluoxetine and sertraline:

Fluoxetine and sertraline are SSRIs that are approved for use as antidepressants, but not for the treatment of obesity. Both fluoxetine (664, 665) and sertraline (666) reduce food intake in experimental animals. During clinical trials to approve these drugs as antidepressants, weight loss was observed. With sertraline weight loss averaged 0.45–0.91 kg in trials lasting 8–16 wk.

Table 13 summarizes data on clinical trials with fluoxetine. Effects on food intake have been reported (667, 668).

Wise (664) reviewed six short-term double-blind placebo-controlled studies with fluoxetine of 6–8 wk duration, only three of which are published elsewhere. He found that fluoxetine (60 mg/day) produced a loss of 0.23 kg/wk more than placebo.

Levine *et al.* (669) reported a dose response to fluoxetine over the dose range 10–80 mg/day. In a study of binge eaters, Marcus *et al.* (130) reported that binge eaters responded as well as non-binge eaters over the 1 yr trial. In a study of diabetics (127, 670), the fluoxetine-treated patients lost more weight and reduced their requirement for insulin.

The principal problem with fluoxetine as an antiobesity agent was the regain in weight observed in long-term clinical trials (126, 675, 676). Darga *et al.* (126) noted a weight loss of 11.7% by 29 wk, but by the end of 1 yr, the weight loss was only 7.8% and not significantly different from placebo. In an analysis of these long-term studies, Saylor *et al.* (114) found that the 504 patients treated with placebo lost 2.1% at 6 months, compared with a 5.3% loss in the 522 subjects treated with fluoxetine. By the end of 12 months of treatment, however, the group taking fluoxetine had lost only 2.7% of their baseline weight, compared with 1.6% in the placebo group.

In an 8-month study comparing fluoxetine 40 mg/day with the combination of fluoxetine 40 mg/day and dexfen-

TABLE 13. Clinical trials with fluoxetine

Author	Year	No. of subjects		Dose of medication (mg/day)	Duration (wk)	Initial wt (kg)		Wt changes (kg)		Met criteria		Comments and conclusion
		Placebo	Drug			Placebo	Drug	Placebo	Drug	FDA	CPMP	
Ferguson and Feighner (119)	1987	50	50	40 60 80	8	93	93	-1.7	-4.8	No	No	Benzphetamine as comparison lost -4.0 kg
Levine <i>et al.</i> (669)	1989	131	131	10 20 40 60	8	97	95	-0.54	-0.94 -1.93 -2.16 -3.91	No	No	Multicenter dose-ranging study
Marcus <i>et al.</i> (130)	1990	No binge Binge	10/13 12/10	60	52	110.0 94.7	92.8 103.9	+0.6	-17.1 -8.4	Yes	Yes	Binge-eaters, 10 centers
Darga <i>et al.</i> (126)	1991	22	23	60	52	102.9	105.8	-4.6	-8.2	No	No	Type 2 diabetics
Gray <i>et al.</i> (127)	1992	24	24	60	24	107.3	105.5	-0.8	-4.2	No	No	Type 2 diabetics
Fernandez-Soto <i>et al.</i> (671)	1995	19	23	60	12	BMI		-8.6	-7.3	No	No	Cross-over
Connolly <i>et al.</i> (672)	1994	11	13	60	24	36.8 92.0	35.1 85.1	0.0	-3.9	No	No	3 mo × 3 mo Elderly >60 yr Type 2 diabetics
O'Kane <i>et al.</i> (673)	1993	9	10	60	52	97.5	97.8	+1.5	-4.3	Yes	No	Type 2 diabetics
Visser <i>et al.</i> (674)	1993	20	18	60	12	89.1	87.7	-2.4	-5.9	No	No	MRI of visceral fat
Goldstein <i>et al.</i> (675)	1993	107 106	104 106	20 60	48	89.1	89.2 84.9	-2.0	-1.7 -3.1	No	No	Multicenter entry after >3.6 kg wt loss on fluoxetine
Goldstein <i>et al.</i> (676)	1994	228	230	60	52	99.2	100.3	-2.1	-1.7	No	No	Multicenter
Daubresse <i>et al.</i> (663)	1996	43	39	60	8	93.0	90.9	-0.9	-3.1	No	No	Multicenter Type 2 diabetics

fluramine 15 mg/day, Pedrinola *et al.* (597) demonstrated that the combination doubled the weight loss seen with fluoxetine alone. A secondary prevention study is the only controlled weight loss trial with sertraline, and results with sertraline were not different from those with placebo (680).

We conclude that SSRIs, *per se*, do not appear to be efficient medications for weight loss, but for those patients who are obese as well as depressed, serotonin reuptake inhibitors may be a more appropriate treatment than other antidepressants that are known to be associated with weight gain such as some of the tricyclic antidepressants. Both sertraline and fluoxetine lose their effectiveness as weight loss drugs with continued administration. This loss of effectiveness is not seen with other drugs, and the basis for this effect is unknown.

*d. Clinical trials with serotonin-NE reuptake inhibitor (SNRI).* Sibutramine is a selective reuptake inhibitor that is most potent for serotonin and NE, but is also blocks dopamine reuptake. Like the drugs acting on individual receptors, sibutramine reduces food intake and probably increases thermogenesis. In clinical trials the drug produces significantly more weight loss than placebo. Its side effects are similar to those of noradrenergic drugs. Patients should be monitored during early therapy in case they have an unexpectedly high rise in blood pressure. Sibutramine has not been reported to produce cardiac valvular insufficiency.

*i) Pharmacology.* In experimental animals the inhibition of food intake by sibutramine is duplicated by combining a noradrenergic reuptake inhibitor (nisoxetine) with a serotonin reuptake inhibitor (fluoxetine) (681). Sibutramine produces the behavioral sequence of satiety (682). Sibutramine does not bind to any one of the wide variety of receptors on which it has been tested. In addition to the inhibition of food intake (684), sibutramine also stimulates thermogenesis in experimental animals (408) and in human beings but, as noted above, the human data are contradictory (470, 471).

*ii) Clinical trials.* Both short-term (121, 682, 683, 685, 691) and long-term (683, 686–690) clinical trials have been reported with sibutramine, and these are summarized in Table 14 and elsewhere (682, 683).

In an 8-wk trial comparing placebo with 5 and 20 mg/day of sibutramine, Weintraub *et al.* (121) noted a weight loss of  $1.4 \pm 2.1$  kg in the placebo group,  $2.9 \pm 2.3$  kg in the group treated with 5 mg/day, and  $5.0 \pm 2.7$  kg in the group treated with 20 mg/day.

Data from one site (687) of a multicenter trial (689) have been published showing a dose-related weight loss lasting up to 6 months (Fig. 13). A total of 173 patients were randomized to receive placebo or 1, 5, 10, 15, 20, or 30 mg/day of sibutramine. There was a clear dose-response effect with the placebo group losing 1% and the 30 mg/day group losing 9.5% of initial body weight. By the end of the 6 months, patients receiving the lower doses had plateaued in their weight loss, but the 15, 20, and 30 mg/day dose groups were still losing weight.

In a 1-yr trial with sibutramine comparing placebo with 10 and 15 mg/day, there was a significantly greater weight loss

in the 10 and 15 mg/day group than in the placebo-treated group (686).

As with dexfenfluramine, the initial weight loss in patients treated with sibutramine predicts long-term response. Of those losing more than 2 kg in 4 wk only 20% of those receiving placebo *vs.* 49% of those treated with sibutramine lost more than 10% of initial body weight in 12 months (689). Weight loss with sibutramine or placebo produces a graded decrease in triglycerides and low-density lipoprotein (LDL) cholesterol. Hanotin *et al.* (691) compared dexfenfluramine 30 mg/day with sibutramine 10 mg/day in 226 subjects in a double-blind multicenter study and found no difference in effectiveness or tolerability. Apfelbaum *et al.* (690) evaluated sibutramine in weight maintenance. They screened 205 patients and randomized to placebo or sibutramine 10 mg/day for 12 months 160 patients who lost at least 6 kg (mean loss  $-7.4$  to  $-7.7$  kg) during 4 weeks on a very low calorie diet (220 to 800 kcal/day). During 12 months from the end of the very low calorie diet baseline, the completing patients treated with sibutramine lost  $-6.1 \pm 8.1$  kg *vs.* a small weight gain of  $+0.5 \pm 5.7$  kg.

*e. Clinical trials using two approved drugs.* Since phentermine causes weight loss through noradrenergic mechanisms and fenfluramine through serotonergic mechanisms, Weintraub *et al.* (122) reasoned that combining the two medications might improve the treatment of obesity by increasing weight loss or reducing symptoms. In an initial 6-month study, 81 subjects were divided into four groups to compare phentermine 30 mg/day, fenfluramine 60 mg/day, and the combination of phentermine 15 mg/day and fenfluramine 30 mg/day against placebo. The three drug-treated groups lost significantly more weight than the placebo-treated group, but were not different from one another. The side effects of the combination were less than any of the single medication groups alone, presumably because the combination of a stimulant with a depressant may cancel some of the side effects. Encouraged by this experience, Weintraub and associates (692–699) designed a 4-yr study that they published as a series of articles in 1992.

The trial consisted of several phases. Phase I was a randomized double-blind placebo-controlled study lasting 34 wk (693). During the first 6 wk a single-blind placebo period used active treatment with diet, exercise, and behavior therapy (Fig. 14, *left half*). Weight loss in these 6 wk averaged 4.2 kg ( $4.5 \pm 0.3$  in active treatment group and  $3.9 \pm 0.4$  in placebo group). The 121 subjects were then randomized using minimization techniques to receive either placebo or fenfluramine (60 mg/day) and phentermine (15 mg/day) for 28 wk in a double-blind trial along with continued diet, exercise, and behavior modification. At the end of 34 wk, the 58 placebo-treated patients had lost  $4.6 \pm 0.8$  kg ( $4.9 \pm 0.9\%$ ) of their initial body weight and the 54 patients remaining in the medication group had lost  $14.2 \pm 0.9$  kg ( $15.9 \pm 0.9\%$ ). Nine of the 121 subjects (7.5%) who entered the study dropped out before the conclusion of the 34-wk treatment period. The main adverse effect was dry mouth.

Phase 2 of the study (weeks 34–104) explored intermittent *vs.* continuous effect of active therapy for those initially randomized to drug, and open-label drug treatment for the

TABLE 14. Clinical trials with sibutramine

Author	Year	No. subjects		Dose (mg/day)	Duration of study (wk)	Initial wt (kg)		Wt loss (kg)		Wt loss (%)		Met criteria		Comments
		Start (P/D)	Completers (P/D)			Placebo	Drug	Placebo	Drug	Placebo	Drug	FDA	CFMP	
Weintraub <i>et al.</i> (121)	1991	20	19	5	8	97	-1.4	-2.9	-1.3	3.0	No	No	Dose-ranging phase II	
		20	18			102.4	-5.0	5.1	No	No				
Jones <i>et al.</i> (686)	1995	163	76	10	52	87	-2.2	-6.2	-2.5	-7.1	No	No	Abstract	
		161	93			87	-6.9	-7.9	Yes	No				
Bray <i>et al.</i> (687)	1996	24		1	24	92.0	-0.75	-2.96	-0.77	-3.20	No	No	Part of multicenter study Data on completing women	
		23				95.8	-2.87	-3.07	No	No				
		24				90.9	-6.19	-6.91	Yes	No				
		25				87.2	-6.89	-7.77	Yes	No				
		25				89.7	-7.30	-8.06	Yes	Yes				
		24				90.9	-8.24	-9.17	Yes	Yes				
Hanotin <i>et al.</i> (688)	1998	59	47	5	12	84	-1.4	-2.4	-1.7	-2.9	No	No	Multicenter trial	
		56				83.3	-5.1	-6.0	No	No				
		59				85.0	-4.9	-5.5	No	No				
		62				88.3	-1.3	-2.7	No	No				
		62				94	-3.7	-3.9	No	No				
Bray <i>et al.</i> (689)	1999	148	87	0	24	95	-1.3	-5.7	-1.2	-6.1	Yes	Yes	Multicenter phase III trial	
		149				95	-7.0	-7.4	Yes	Yes				
		151				107	-8.2	-8.8	Yes	Yes				
		150				99	-9.0	-9.4	Yes	Yes				
		152				98	+0.2	-6.4	Yes	Yes				
		146				96	-6.1	-6.4	Yes	Yes				
		151				101	-9.0	-9.4	Yes	Yes				
Apfelbaum <i>et al.</i> (690)	1999	181	48	10	52	97.7	+0.2	-6.1	+0.2	-6.4	Yes	No	Multicenter wt loss $\geq$ 6 kg on 4 wk VLCD randomized	
		82	60			95.7	-6.1	-6.4	Yes	No				

FIG. 13. Effect of sibutramine on body weight. There was a dose-dependent reduction in body weight over the 24 weeks of the trial. [Adapted with permission from G. A. Bray *et al.*: *Obes Res* 7:189–198, 1999 (689).]

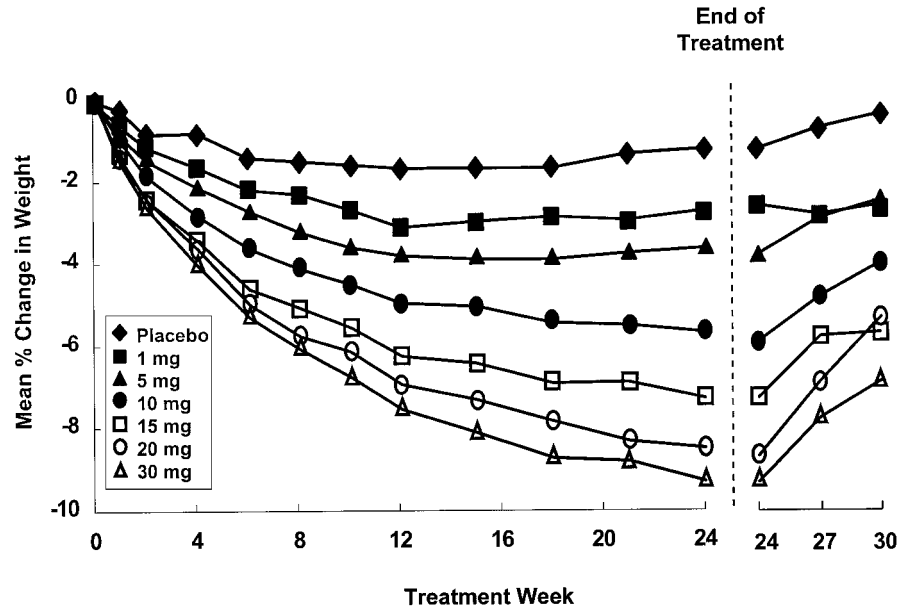
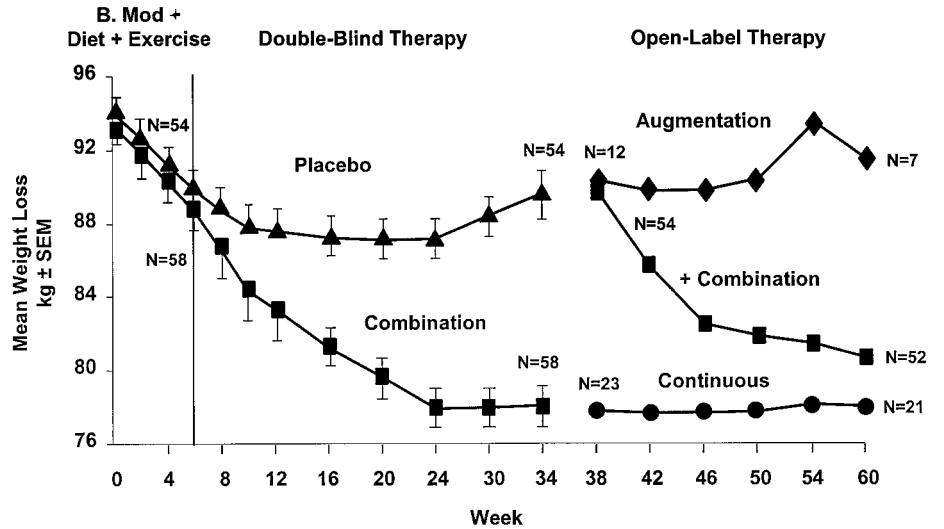


FIG. 14. Effect of fenfluramine and phentermine on weight loss. Participant body weight (kg) by study week. *Open circles* represent placebo group mean  $\pm$  [scap]sem (n = 54). *Open squares* represent fenfluramine plus phentermine group mean  $\pm$  SEM (n = 58). [Adapted with permission from M. Weintraub *et al.*: *Clin Pharmacol Ther* 51:586–594, 1992 (693) and *Clin Pharmacol Ther* 51:595–601, 1992 (694).]



NOTE: 130 run-in patients; 121 randomized; 112 34-week completers.

initial placebo group (694). The effectiveness of an augmented dose was evaluated in 12 patients who did not respond to the initial treatment. Subjects gained weight during the times that they were not receiving medication and lost weight to the level of the continuous medication group when they were on medication. By the end of phase 2 (week 104), only 83 (68%) of the initial patients were still in the program. At the end of phase 2, average weight loss was  $10.8 \pm 0.7$  kg ( $11.6 \pm 0.8\%$ ). Intermittent and continuous therapy produced identical weight loss (11.6 kg), whereas those on augmented therapy were less successful ( $-6.5 \pm 1.5$  kg weight loss). Augmentation of the medication dose did not seem to improve weight loss in this subgroup.

Phase 3 (104–156 wk) was an open-label dose-adjustment phase (695). Those who completed this phase (n = 59) had regained  $2.7 \pm 0.5$  kg, but were nonetheless  $9.4 \pm 0.8$  kg below baseline. Phase 4 was a second double-blind random-

ized trial (weeks 156–190) (696). Here again, the drug-treated patients maintained weight loss better than the placebo-treated group who regained weight. Those treated with drug (n = 27) gained significantly less ( $4.4 \pm 0.5$  kg or  $5.3 \pm 0.5\%$ ) than the placebo-treated patients (n = 24) ( $6.9 \pm 0.8$  kg or  $8.5 \pm 1.1\%$ ). At week 190, the beginning of phase 5, medication was discontinued (697). After more than 3.5 yr of treatment with fenfluramine and phentermine, there was some weight regain in all the groups, but the group receiving two medications maintained a lower weight ( $-5.0 \pm 1.4$  kg) than those on placebo ( $-2.1 \pm 1.2$  kg) (697). There were 51 subjects remaining in the study at the end of 190 wk, for a drop-out rate of 58% over more than 3.5 yr. When medication was stopped, the drug-treated group regained weight faster than the group that had been on placebo, showing that the drugs were effective when used but that they did not cure obesity. Lipids and blood pressure improved in those who

lost weight (698). This study demonstrated that two medications could achieve medically significant weight loss with few side effects over 3.5 yr. There was a slow, upward creep of weight in both the drug- and placebo-treated groups over this period, but this may represent the natural history of obesity. No other controlled trials with two drugs have yet been published.

Two open-label, uncontrolled studies of fenfluramine and phentermine in a private practice have been published. Atkinson *et al.* (700) reported a 16.5-kg weight loss in 1,197 patients at 6 months. This weight loss was maintained at 18 months. Of this cohort, 298 had a BMI > 40 kg/m<sup>2</sup>. Approximately one-half completed 1 yr of treatment while about one-third completed 2 yr. Weight loss was 17.9% of initial body weight at both time points (700). In a second study, 96 subjects that were treated with fenfluramine and phentermine after losing weight during treatment with a very-low-calorie diet for an average of 16.5 wk (701). These subjects lost 16.2% of initial body weight on the very-low-calorie diet and 9 months after starting drugs had lost an additional 2.9% of initial body weight. Because one-third to one-half of the weight loss was regained at 3 yr in the study by Weintraub *et al.* (122) and because a double-blind randomized placebo-controlled study with phentermine and fenfluramine after 3 yr of treatment with that same combination of medication demonstrated a slower weight regain on the medication, it is reasonable to conclude that the medication does not lose its effectiveness, and that obesity is a slowly progressive disease.

*f. Prevention of weight regain (2° prevention).* Several double-blind, randomized, placebo-controlled studies have compared the effect of drugs or placebo in helping maintain weight loss induced in an initial open-label trial. These studies have used *d,l*-fenfluramine, dexfenfluramine, fluoxetine, sertraline, and sibutramine. In the first reported study of this type, Douglas *et al.* (657) treated a group of obese women with *d,l*-fenfluramine for up to 26 wk. The women who lost 6 kg or more in 26 wk were randomized to receive either *d,l*-fenfluramine 60 mg/day or placebo for a further 26 wk. Of the group treated with *d,l*-fenfluramine, 38% maintained their weight loss, compared with only 9.5% of those treated with placebo.

Finer (646) used a similar design, but induced the initial weight loss with a very-low-calorie diet for 8 wk before beginning the randomized placebo-controlled trial of dexfenfluramine for 6 months in 45 subjects. During 8 wk on the very-low-calorie diet, patients lost 11–12% of initial body weight. The patients randomized to placebo maintained their weight loss for a few weeks but by the end of the trial had regained 2.9% of their initial body weight. In contrast, the patients randomized to dexfenfluramine lost an additional 5.8% of their initial body weight. The study by Noble (Table 12) (438) used subjects who lost more than 4.5 kg before randomization and might also be considered a 2° prevention trial.

A 2° prevention trial with sertraline, a SSRI, failed to prevent weight regain (680). Wadden *et al.* studied a group of 53 women who had lost an average of 22.9 ± 7.1 kg while adhering to a very-low-calorie diet; these women were ran-

domized to receive either placebo or sertraline, 200 mg/day, for a 54-wk trial. During the first 6 wk, sertraline-treated patients lost an additional 5.1% (1.0 kg) of their body weight. Thereafter, the body weight of both groups rose. At the end of 54 wk the placebo group were still 11.7% below their initial starting weight compared with 8.2% in the sertraline-treated group.

Goldstein *et al.* (675) reported a multicenter trial in which 317 subjects were treated with fluoxetine 60 mg/day for 8 wk and achieved a 7.2% loss of initial body weight. He then randomized the patients into three groups that were treated for 40 wk. Of these subjects, 107 received placebo, 104 received fluoxetine 20 mg/day, and 106 received fluoxetine 60 mg/day. At the end of the study the weight loss by the three groups was not different and had maintained a loss of about 2.1% of initial body weight from baseline.

A 2° prevention trial of sibutramine has been reported by Apfelbaum *et al.* (690) and in the FDA-approved package insert. Obese patients initially lost weight and were randomly assigned to placebo or sibutramine for 12 months. The drug-treated group continued to lose weight, whereas the placebo-treated group had a significant regain from their nadir (698).

*g. Predictors of success.* There is a wide spectrum of response to antiobesity drugs. This variability of weight loss may reflect differences in patient compliance as well as individual differences in response to the medication.

When identical diets given to inpatient and outpatient groups are compared, the rate of weight loss in the outpatients is slower than observed with the inpatients, in spite of the greater activity associated with being an outpatient subject. This implies a reduction in compliance with diet in outpatients (645, 703). Variable compliance was also noted in the INDEX study (587, 652, 653). Patients randomized to dexfenfluramine treatment with no measurable *d*-fenfluramine and *d*-norfenfluramine in their plasma at the 6-month visit had weight losses identical with the placebo-treated patients. Increasing blood levels were associated with increasing weight loss. Innes *et al.* (635) reported similarly that women with plasma fenfluramine and norfenfluramine levels of 200 ng/ml lost a mean of 8.8 kg compared with a loss of 2.1 kg in women with concentrations less than 100 ng/ml (635). Phentermine blood levels, on the other hand, did not correlate with weight loss (554).

Initial rate of weight loss has been a frequently noted predictor of subsequent weight loss (593, 689). Those who lose more than 2 kg in the first month are more likely to succeed. Age is another predictor, with each additional 10 yr of age being associated with an increased weight loss over 3 months of approximately 1 kg (584). Weintraub *et al.* (704) also identified predictors of success.

*h. Safety of noradrenergic and serotonergic medications.* A number of side effects have been reported with the available noradrenergic and serotonergic drugs. Amphetamine is an addictive drug that should not be used for treating obesity, but the other appetite-suppressing drugs have little (amphetamine, diethylpropion, mazindol, phentermine, or phendimetrazine) or no (sibutramine, PPA) abuse potential.

Neuroanatomical changes have been reported when high doses of fenfluramine or dexfenfluramine have been given parenterally, but comparable data in humans do not exist. Primary pulmonary hypertension (PPH) is a rare disease initially reported with use of aminorex, which led to its recall more than 25 yr ago. Rare cases of pulmonary hypertension have been reported in association with fenfluramine. The major problem with the noradrenergic and serotonergic drugs has been the appearance of cardiac valvular insufficiency in patients treated with fenfluramine and phentermine (2, 702). The rate of this complication is as high as 32%.

*i) Side effect profile:* From the clinical trials in which placebo groups are included it is possible to identify the side effect profile for the appetite suppressants. Dry mouth, asthenia, reduced appetite, and insomnia are the principal reported side effects. The effect on sleep of fenfluramine and the noradrenergic drugs differ. Diethylpropion was clearly a stimulant producing frequent awakenings, delay of paradoxical [rapid eye movement (REM)] sleep, and increased time in stage 1 (drowsiness) (705). The same is true of *d*-amphetamine (706–708) and phentermine (708). Fenfluramine, on the other hand, did not affect awakenings or REM sleep, but did cause frequent shifts into stage 1 sleep (705).

Emotional symptomatology, such as anxious or anxious-depressive symptoms, were more effectively alleviated by fenfluramine or by *d*-amphetamine than by placebo (610). These are usually mild and rarely lead to termination of treatment. For the agents with sympathomimetic properties (benzphetamine, phendimetrazine, phentermine, diethylpropion, mazindol, and sibutramine) constipation is a common complaint. For the serotonergic drugs (*d,l*-fenfluramine and dexfenfluramine), the incidence of diarrhea or loose bowels is reported. Among the other side effects are abdominal pain, anxiety, delusions, and dizziness.

Five issues of a more serious nature must also be included in decisions to use medications. These are the reports of drug abuse and addiction, of neuronal changes, of the serotonin syndrome, of PPH, and of valvular heart damage.

*ii) Abuse potential:* Evaluation of abuse potential can be done with several techniques (709). The reinforcing properties of anorectic drugs have been one of the techniques used to evaluate abuse potential. In rats, phenmetrazine, diethylpropion, and phentermine have reinforcing properties as assessed by self-administration of these drugs. Fenfluramine, on the other hand, is not reinforcing (710–712). In baboons, cocaine, chlorphentermine, and diethylpropion are reinforcing, but fenfluramine is not (713). Amphetamine and diethylpropion also reduced food intake and maintained responding in rhesus monkeys (714, 715).

Noradrenergic drugs have been divided by the US government for regulatory purposes into categories purported to represent their potential for CNS stimulation and abuse. Compounds in category II, amphetamine, methamphetamine, and phenmetrazine, have clearly been abused (713). The Drug Abuse Warning Network (DAWN) listing of various anorectic drugs compiled from emergency room visits does not list either benzphetamine or phendimetrazine as abused drugs in the last 10 yr (716, 717) (Table 15). This table lists the rank order in 1988 and 1994 of some abused substances. Seven of the drugs discussed in this review appear

TABLE 15. Relative frequency of various drugs mentioned by emergency rooms in the 1994 drug abuse warning network (716, 717)

Drug	1998		1994	
	Rank	%	Rank	%
Alcohol-in-combination			1	31
Cocaine	1	38.80	2	27.55
Aspirin	8	3.46	6	3.73
Ibuprofen			7	3.67
Methamphetamine/speed	11	1.89	8	3.41
Amphetamine	22	0.82	14	1.86
Fluoxetine			17	1.76
Caffeine	44	0.32	35	0.61
Ephedrine			48	0.46
OTC diet aids	52	0.27	52	0.37
Theophylline			55	0.32
Phenylpropanolamine	116	0.06	105	0.09
Diethylpropion	223	0.01		

OTC, Over the counter.

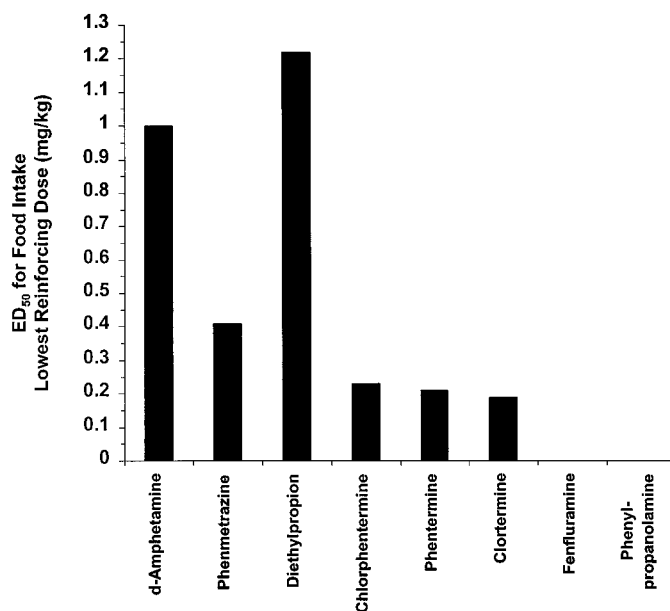


FIG. 15. Ratio of ED<sub>50</sub> for food intake to lowest reinforcing dose. [Derived from (719).]

on the list. Methamphetamine, *d*-amphetamine, and PPA appear in both years. Figure 15 compares the ratio of the 50% reduction in food intake to the lowest reinforcing dose in baboons. Two drugs, fenfluramine and PPA, are not abused in this baboon model (718, 719).

Abuse potential has also been studied in people. *d,l*-Fenfluramine and *d*-amphetamine have been compared in eight postaddict volunteers. Fenfluramine overall was unpleasant and sedative although it produced euphoria in some subjects. Amphetamine and fenfluramine were qualitatively different, leading Griffith *et al.* (428) and Locke *et al.* (720) to conclude that fenfluramine is not amphetamine-like. Sibutramine is a Schedule IV drug, but in experimental animals, it does not have reinforcing properties (721). PPA has no potential for abuse and the abuse potential of caffeine is equivocal. The abuse potential for ephedrine, while low, does exist (Table 14). In studies with self-administration, *d*-amphetamine is preferred more than diethylpropion and both are preferred



more than placebo (722). Although abuse in humans is clear, particularly with *d*-amphetamine, methamphetamine, and phenmetrazine (723), it is unclear whether overweight individuals treated with these drugs are as likely to become addicted as individuals of normal weight (724).

*iii) Serotonin syndrome:* Combination of fenfluramine or dexfenfluramine with other serotonergic drugs such as serotonin reuptake inhibitors, sumatriptan, dihydroergotamine, or melatonin can produce the "serotonin syndrome." This consists of one or more of the following symptoms: excitement, hypomania, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, motor weakness, myoclonus, tremor, hemiballismus, hyperreflexia, ataxia, dysarthria, incoordination, hyperthermia, shivering, pupillary dilatation, diaphoresis, emesis, and tachycardia. Treatment consists in appropriate support and withdrawal of the drug (725).

*iv) Neuroanatomic changes:* Acute doses of dexfenfluramine in animals that produce 10 times the brain concentrations seen in humans have been associated with decreased brain serotonin concentrations that last for weeks to months (726–732). However, studies of neuronal function that used techniques that are independent of serotonin content such as retrograde transport, silver staining, and glial fibrillary acidic protein content did not detect neuronal damage at doses of dexfenfluramine that resulted in decreased brain serotonin content (730). In squirrel monkeys (727), brain serotonin content was decreased for 14–17 months after a 4-day treatment regimen that achieved brain serotonin concentrations 35 times those seen in obese humans taking usual therapeutic doses. Fenfluramine caused marked reductions in serotonin-specific binding in regions of the baboon brain on positron emission tomography, a method that could be applied to living humans (728). Although all animal species tested by all routes of administration have shown decreased brain serotonin concentrations with acute high-dose administration of dexfenfluramine, the same is not true for escalating dose regimens. A 2-yr study in mice achieving brain concentrations of serotonin 12 times that seen in humans produced no change in brain serotonin concentration or in the number of serotonin transporters (730). Although reductions in brain serotonin concentrations are usually reversible, this may depend in part upon the dose. There were no changes in animal behavior associated with decreased brain serotonin concentrations, and clinical use has not been associated with reported changes in behavior.

*v) PPH:* An outbreak of cases of pulmonary hypertension after the introduction of aminorex (Menocil) to treat obesity in 1967–1972 was the first documentation of a relationship between  $\beta$ -phenethylamines and PPH (plexogenic arteriopathy) (12). PPH is a rare disease that occurs with a frequency of about 1–2 per million persons per year (733). Obesity increases the risk by 2- to 3-fold, and it is further increased with anorectic medication. A retrospective case-control study including 95 cases from several European centers and 355 matched controls estimated that the use of appetite-suppressant medications may have increased the odds ratio to between 10 and 23 for an incidence to 28–43 per million per year (733). Kramer and Lane (13) reexamined the data from the aminorex cases to provide a comparison with fen-

fluramine. They estimate the odds ratio for developing PPH after exposure to aminorex was 97.8 (95% CI = 78.9–121.3) and that nearly 80% of the cases of PPH in the affected countries could be attributed to aminorex. Using the French and Belgian cases in the dexfenfluramine study (733), they estimated the odds ratio for developing PPH after exposure to dexfenfluramine to be 3.7 (95% CI = 1.9–7.2) for 3 months or more exposure and 7.0 (95% CI = 2.8–17.6) for exposures lasting more than 12 months (12). Dexfenfluramine, in contrast to aminorex, was estimated to increase the background rate by 20% or less.

Dexfenfluramine has been demonstrated to increase pulmonary vascular resistance in dogs similar to the effect of hypoxia but separate from it (734). Aminorex, fenfluramine, and dexfenfluramine also inhibit potassium current in rat pulmonary vascular smooth muscle causing pulmonary vasoconstriction. Inhibition of nitric oxide production enhances vasoconstriction, suggesting that susceptibility to PPH may be associated with decreased endogenous nitric oxide production (735). After the release of dexfenfluramine in the United States, one fatal case of pulmonary hypertension was reported (736). Based on an evaluation of the risk-benefit ratio at the time of release, Manson and Faich (737) concluded the balance was tipped in favor of the drug when used appropriately.

*vi) Valvular cardiac lesions in patients treated with fenfluramine and phentermine:* Connolly *et al.* (2) reported a series of 24 female patients who were referred to evaluate symptoms of dyspnea, edema, or a heart murmur, and many more have been reported since (702). These women were young [mean age  $43.5 \pm 7.9$  yr] and all of them had been on the combination of phentermine and fenfluramine [mean length of treatment  $12.2 \pm 6.8$  months]. On echocardiogram, all the women had thickening of the valvular leaflets and valvular insufficiency. Five women required heart valve replacement, and at surgery, the valves in three were typical of those seen with ergotamine toxicity or with the carcinoid syndrome, states in which serotonin is increased. All of these women had been taking phentermine with fenfluramine, and none had taken ergot alkaloids or had evidence of the carcinoid syndrome. After this initial report, the FDA learned of an additional 28 patients who had been gleaned from a FDA advisory (738). All were women with a median age of 45 (range 28–61 yr) and a median duration of treatment of 10 months (range 2–36). The mitral valve was affected in 86%, the aortic valve in 68%, the tricuspid valve in 39%, and the pulmonary valve in only 4% (1 patient). The valvular disease did not resolve. Doses above 30 mg/day for either fenfluramine or phentermine were more often associated with multivalvular disease (738). Wadden reported a 30% incidence of mild or greater aortic or moderate or greater mitral insufficiency in a group of 21 women treated with phentermine and fenfluramine for 2 yr (739).

Since dexfenfluramine is more specific for the central serotonergic system and phentermine slows serotonin metabolism in the lung, these valvular lesions may be mainly limited to the fenfluramine-phentermine combination, although four patients treated with dexfenfluramine alone were reported to the FDA (738). Due to the rarity and specificity of the valvular lesions, the authors concluded that

there was an association between the lesions and the use of fenfluramine and phentermine in combination. The incidence of valve problems in the United States is about 5–10%. In a prospective study of 86 patients, 7 (8%) were found to have aortic valve lesions before drug therapy (702). Of those with normal values, 13 (16.5%) developed new lesions, all involving the aortic valve and some involving both aortic and mitral valves. We recommend that any patient treated more than 6 months with fenfluramine/phentermine combination should receive prophylactic antibiotic therapy as recommended by the American Heart Association and should consider an echocardiogram.

*vii) Hypertension:* PPA is an  $\alpha_1$ -agonist and as such can cause vasoconstriction and increase blood pressure. Clinical trials (564, 571) show this to be a small problem when the drug is used at recommended levels. The other sympathomimetic drugs can all increase blood pressure, but the effect usually resolves with weight loss. Sibutramine is an exception (689). It produces a small 3–5 mm Hg elevation in blood pressure and a 2–4 beat/min increase in heart rate that lasts as long as the drug is taken.

*4. Peptide neurotransmitters and neuromodulators.* Peptides released in the brain can increase or decrease food intake. Unraveling this area of neuroendocrinology is one of the most rapidly changing areas in the field of obesity research. Neuropeptide Y, opioids, galanin, GH-releasing hormone, melanin concentrating hormone, and orexin (hypocretin) all increase food intake. A second group, including MSH derived from POMC, CRH and its relative urocortin, calcitonin gene-related peptide (CGRP), glucagon-like peptide-1 (GLP-1), oxytocin, cyclohistidyl-proline, neurotensin (NT), and cocaine-amphetamine regulated transcript (CART) reduce food intake. A proposed relationship between these peptides is described in Fig. 16.

All of the FDA-approved appetite-suppressant medications for treatment of obesity act through the monoamine system. The level of understanding for these mechanisms is greater than for the newer peptide-related modulators of feeding. In contrast to the four monoamines and their receptors, there is a long list of peptides that can increase or decrease food intake by acting on receptors in the CNS (Tables 4 and 5). Yet it is through modulation of these peptides by drugs that we see one of the bright hopes for the future of drug treatment in obesity.

The peptides that are involved in the transduction of afferent messages into efferent signals for the motor pattern generator that drives the systems for food seeking and food selection and for the metabolic processes that handle the ingested food can be divided into two groups. One group of peptides increase food seeking and may selectively affect nutrient preferences. A second and larger group of peptides decrease food intake and may likewise have macronutrient specificity for the nutrients they decrease.

*a. Peptides acting centrally that increase food intake.*

*i) Neuropeptide Y:* Neuropeptide Y is a 36-amino acid peptide that is one of the most potent stimulators of food intake known (740). Chronic administration of NPY will produce weight gain. It also produces a dose-dependent decrease in sympathetic activity to brown adipose tissue (741–743). NPY

primarily stimulates the intake of carbohydrate and accomplishes this effect primarily through receptors in the PVN (744–745). These effects of NPY are blocked by antibodies to NPY or by antisense oligonucleotides to NPY synthesis (746). It is interesting that targeted disruption of NPY does not affect food intake or body weight (747). A transgenic mouse deficient in NPY does not show any alteration in body fat or feeding, suggesting that the NPY system may be sufficient to modify feeding but that it is not essential (748). However, NPY knock-out animals are more susceptible to convulsions. At least five receptors for NPY have been identified. Y-5 is currently thought to be the main receptor for NPY and feeding. Antagonists to this receptor might have clinical value.

The NPY circuit involved in feeding originates in the ARC nucleus with its first relays in the PVN and perifornical area (749). The level of NPY in the ARC nucleus is decreased by treatment with leptin (750) and increased by starvation and diabetes (751). The perifornical area of the medial hypothalamus appears to be most responsive to NPY. NPY is located in many regions of the brain as well as in peripheral tissues and it is cosecreted with NE in many, but not all, circumstances. Antagonists to the effect of NPY have been identified (751) and offer promise for therapeutic treatment of obesity. NPY produces reciprocal effects on food intake and gonadotropin secretion and reproductive function probably through receptors other than Y-5 (752).

Stimulation of food intake by injection of NPY into the PVN is blocked by parenteral injection of naloxone but not by injection of naloxone into the PVN. When naloxone is injected into the hindbrain, on the other hand, the stimulation of food intake when NPY is injected into the PVN is blocked, suggesting that there is an opioid receptor system activated by NPY in the PVN that has opioid receptors in the hindbrain (753).

*ii) Opioids:* Both dynorphin (299) and  $\beta$ -endorphin (300) stimulate food intake when injected into the ventricular system of the brain. These effects can be blocked by antagonists to  $\kappa$ -opioid receptors. Stimulation of  $\kappa$ -opioid receptors increases fat intake, which can be blocked by  $\kappa$ -opioid antagonists (754). Naloxone, an antagonist to opioid receptors, reduces fat intake (755) and interferes with the feeding effects of NPY (753).

After the observation that naloxone could produce a reduction in food intake in normal subjects (756), naltrexone, a longer-lasting derivative, was tried in several clinical trials (757–764). The results of these trials were disappointing, and naltrexone has not been tried at the higher doses that might be required to produce a reduction in weight because of its potential for hepatic toxicity. A number of opioid antagonists are known but none have gone into clinical trial.

*iii) Galanin:* Galanin is a 29-amino acid peptide isolated from both the GI tract and brain (765, 766). Injection of galanin into the third ventricle of the brain or into the PVN will increase food intake (767, 768). Some studies have suggested that this peptide preferentially stimulates fat intake (769), but others show that these effects on fat intake occurred because animals were fat-preferring animals and that galanin merely stimulated the underlying food preference of the animal (770). Galanin stimulates feeding when injected into the hindbrain as well as the PVN, and these effects of galanin in

both the third ventricle and hindbrain can be blocked by M-40, a peptide antagonist to galanin (771). Galanin antagonists are thus potential targets for therapeutic agents, acting on one or more of its receptors (772) although chronic treatment with galanin does not increase body weight.

*iv) GH-releasing hormone (GHRH) and SRIF:* GHRH and SRIF are both released into the hypothalamic portal vein system and respectively stimulate (GHRH) or inhibit (SRIF) GH release from the pituitary. At low doses, each of these peptides has been purported to increase food intake, and GHRH has been reported to selectively increase protein intake (773, 774). A synthetic GH-releasing peptide (KP-102) has also been reported to increase food intake (775).

*v) Melanin concentrating hormone (MCH):* MCH is a cyclic 19-amino acid peptide whose mRNA is exclusively expressed in the zona incerta and lateral hypothalamus (776). Injection of 5  $\mu$ g of MCH into the lateral ventricle significantly increased food intake of experimental animals. MCH and  $\alpha$ -MSH are antagonistic on feeding. The location of the peptide in the lateral hypothalamus suggests that it may be involved in modulating food intake (777, 778). Additional support for this idea comes from the finding that the message for MCH expression was increased in the hypothalamus of the *ob/ob* (leptin-deficient) mouse (303).

*vi) Orexin:* Orexin A and B (305) which were independently called hypocretin (306) are the same molecule and new additions to the list of peptides that stimulate food intake. Isolated as endogenous ligands for orphan G protein-coupled receptors, these peptides are effective stimulators of food intake. Their location in the lateral hypothalamus provides a new basis for understanding why lesions in this area of the hypothalamus (779, 780) reduce food intake.

*b. Peptides acting centrally that decrease food intake.*

*i) MSH:* The methylation of MSH, a 13-amino acid peptide produced by the posttranslational processing of POMC (781), dramatically modifies its effect on food intake (782). Injection of the nonacetylated form of MSH into the third ventricle has no effect on food intake, whereas the acetylated form,  $\alpha$ -MSH, reduces food intake probably by acting on melanocortin-3/4 receptors in the brain. The agouti-signaling protein, which is overproduced in the yellow obese mouse, probably produces obesity by competing with  $\alpha$ -MSH at these receptors (783). The importance of the melanocortin receptors in control of food intake has been amplified by three recent studies. An agonist to the melanocortin receptor will inhibit food intake in several mouse models of hyperphagia, including the leptin-deficient *ob/ob* (*Lep<sup>ob</sup>*) mouse, mice injected with NPY, overnight fasted mice, and in the *yellow* (*A<sup>vy</sup>*) mouse (784). Second, identification of an agouti-related peptide in the hypothalamus that might be involved in modulation of the melanocortin receptor (785) provides an understanding of how the  $\alpha$ -MSH inhibitory signal can be modulated. The agouti-related protein (AGRP) derived from the hypothalamus transcript is a potent antagonist of the melanocortin 3 and melanocortin 4 receptors (786). Third, gene targeting to disrupt the melanocortin-4 receptor in the brain of mice resulted in major weight gain and obesity (787). A clinical syndrome of obesity, adrenal insufficiency and red hair pigmentation, results from defects

in POMC (788). These data suggest that this system may be a productive one for pharmacological intervention. Drugs that act on the MC3/4-R receptors are potentially valuable prospects.

*ii) CRH and urocortin:* CRH may have many roles, three of which are relevant here (789, 790). First, it is the peptide that is secreted from the PVN into the hypothalamic portal system to stimulate ACTH release from the pituitary gland. Second, CRH modulates the function of the autonomic nervous system, including inhibition of the parasympathetic nervous system and activation of the peripheral components of the sympathetic nervous system that increase thermogenesis (791, 793). Third, CRH has a variety of effects on exploratory and other behaviors. Chronic infusion of CRH into the ventricular system will reduce weight gain in both obese and lean experimental animals (792, 793). Overexpression of CRH in a transgenic mouse increases food intake (794).

Urocortin is a member of the CRH family, but its location in the lateral hypothalamus and several other brain regions is different from CRH. It has a higher affinity for the CRH-2 receptors, and its distribution corresponds to the distribution of these receptors. Urocortin produces a dose-dependent decrease in food intake and is considerably more potent than CRH. At doses that depress food intake, urocortin does not produce the angiogenic effects seen with CRH (324).

*iii) Calcitonin and its gene-related peptide (CGRP):* Modulation of calcium can affect food intake. Calcium availability can be manipulated by injecting calcium, altering calmodulin, or by injecting calcitonin. Calcitonin and its gene-related peptide both decrease food intake (795), presumably by making calcium more available and thus possibly modulating ion channels.

*iv) GLP-1:* GLP-1 is the 6–29 fragment of glucagon and is processed in brain and intestine (796). Injection of GLP-1 into the CNS has been reported to decrease food intake whereas exendin, an antagonist to GLP-1 receptor, increases food intake and weight gain (270, 326, 796, 797). Chronic infusion of GLP-1 will reduce food intake and body weight (798). The importance of these findings has been questioned since GLP-1 is aversive (799). Moreover, gene targeting to knock out the GLP-1 receptor (800) does not affect food intake or body weight of mice but does impair the incretin function of GLP-1.

*v) Oxytocin and vasopressin:* An oxytocin pathway modulating food intake under stressful circumstances has been identified (801). Activation of this pathway can also reduce sodium intake. A possible role in the normal control of feeding is suggested by the increase in oxytocin after treatment with fenfluramine.

Arginine vasopressin will also reduce food intake, which may be related to stimulation of the sympathetic nervous system (802). Whether these peptides, whose major role is in lactation and control of renal water excretion, are viable targets for pharmacological development in an antiobesity program is doubtful.

*vi) Cyclo-histidyl-proline (cyclo-his-pro):* Cyclo-his-pro, the carboxy-terminal two amino acids of TRH, is also effective in reducing food intake (803). It was initially thought that cyclo-his-pro was formed from TRH, but its distribution in the brain and gut suggests that it is formed separately. A variety

of derivatives of cyclo-his-pro have been synthesized but are less potent than the dipeptide (804). Cyclo-his-pro and cyclo-asp-pro, derived from enterostatin, both decrease food intake when injected peripherally or centrally, but cyclo-asp-pro is more potent and is more specific in suppressing fat intake.

vii) *NT*: NT injected into the ventricular system of the brain has only weak effects on feeding (327, 805). However, the rise of NT in the circulation after a meal suggests that it may have some peripheral involvement in satiety. Rats equipped to self-stimulate will do so for injections of NT into the ventral tegmental area. The colocalization of NT with dopamine suggests that it may play a role in modulating mesolimbic messages from dopaminergic signals (805, 806).

viii) *CART*: A gene regulated by cocaine and amphetamine, CART, has been identified in the hypothalamus by differential display and directional tag PCR subtraction. CART mRNA is reduced in the ARC nucleus of Zucker fatty rats and *ob/ob* mice and is reduced by starvation in normal rats. One of the peptides processed from CART (CART 55–102) has an amino terminus that is identical to SRIF (807). Administration of CART 55–102 centrally inhibited food intake of nonfasted rats and in NPY-treated rats (324).

#### IV. Drugs That Alter Metabolism

##### A. Preabsorptive agents

Alteration of metabolic processes is the second broad group of mechanisms for drugs that might treat obesity. The only clinically tested one is orlistat, a modified bacterial product that inhibits intestinal lipase and can reduce fat absorption by approximately 30% in subjects eating a 30% fat diet. A number of 1- and 2-yr clinical trials have been reported with this drug. Drug-treated patients lost nearly 10% compared with a loss of 5–6% in the placebo-treated groups. The drug has been approved in most countries including the United States.

##### 1. Orlistat.

a. *Pharmacology*. Orlistat is the hydrogenated derivative of lipstatin that is produced by the bacterium *Streptococcus toxytricini* (808, 809). This compound is highly lipophilic and is a potent inhibitor of most, if not all, mammalian lipases (808–810). The  $\beta$ -lactone ring structure is essential for activity since opening this ring destroys it. Pancreatic lipase is a 449-amino acid enzyme that shares with other lipases a folded structure that is inactive. In the folded state, the N-terminal domain contains the catalytic site that includes serine, histidine, and aspartate. Binding of the enzyme to triglyceride is facilitated by colipase in the presence of bile salts. This interaction serves to expose the active site by opening the lid. One view of this is as though a lid were moved away from the active site by the interaction of the colipase and triglyceride in the bile salt milieu. Orlistat attaches to the active site of the lipase once the lid is opened and in so doing creates an irreversible inhibition at this site. In contrast to its inhibition of lipases, orlistat does not inhibit other intestinal enzymes, including hydrolases, trypsin, pancreatic phospholipase A<sub>2</sub>, phospho-inositol-specific phospholipase C, acetylcholinesterase, or nonspecific liver car-

boxyesterase. Its very small absorption (811, 812) has no effect on systemic lipases.

During short-term treatment with orlistat, fecal fat loss rises during the days of treatment and then returns to control levels after the medication is discontinued, as would be expected from an inhibitor of intestinal lipase (811, 813, 814). With volunteers eating a 30% fat diet, there is a dose-related increase in fecal fat loss that increases rapidly with doses up to 200 mg/day and then reaches a plateau with doses above 400–600 mg/day. The plateau is at approximately 32% of dietary fat lost into the stools. Because the drug partially inhibits triglyceride digestion, it is possible that nutrients or drugs might be less well absorbed (811). Because of its lipid solubility, less than 1% of an oral dose is absorbed and degraded into two major metabolites (815). Pharmacodynamic studies suggest that orlistat does not affect the pharmacokinetic properties of dioxin (816), phenytoin (816), warfarin (817), glyburide (817), oral contraceptives (818), or alcohol (808). Orlistat also did not affect a single dose of four different antihypertensive drugs, furosemide, captopril, nifedipine (816), or atenolol (819). Absorption of vitamins A and E and  $\beta$ -carotene may be slightly reduced (815, 816), and this may require vitamin therapy in a small number of patients.

b. *Clinical trials*. Both short-term (123a) and long-term trials (821–830) with orlistat have been reported. In the first reported 12-wk trial on 44 randomized patients, the drug-treated patients lost 4.3 kg compared with 2.1 kg in those receiving placebo ( $P = 0.025$ ) (123a). In the second short-term multicenter double-blind placebo-controlled clinical trial lasting 12 wk, which was conducted in Europe, 188 patients were randomized to one of three doses of orlistat or placebo. Weight loss in the placebo-treated group was 2.98 kg compared with 3.61 kg in the group receiving orlistat 10 mg three times daily; 3.69 kg in the group receiving 60 mg three times daily; and 4.74 kg in the highest-dose group receiving 120 mg three times a day (123a). In a 6-month multicenter dose-ranging study, orlistat in doses of 30, 60, 120, and 240 mg three times a day produced dose-dependent reductions in body weight of obese patients. Mean levels of fat-soluble vitamins remained in reference ranges (830).

Several double-blind randomized placebo-controlled trials lasting 1 and 2 years have been conducted and data published in papers or in abstract form. Table 16 summarizes the available data. The design of the trials lasting 2 yr followed two formats. They all included a 4- to 5-wk single-blind run-in period after which subjects were stratified into those losing  $\geq 2$  kg or  $< 2$  kg. Orlistat was given at a dose of 60 or 120 mg before each of three meals. The diet contained 30% fat and during the first year was designed to produce a mild hypocaloric deficit of 500 to 600 kcal/day. During the second year patients were placed on a "eucaloric" diet to evaluate the effect of orlistat on weight maintenance. Weight loss at 1 yr varied from 5.5% to 6.6% of initial body weight in the placebo group and 8.5% to 10.2% in the orlistat-treated group. During the second year patients were kept on the same drug regimen as in the first year in two trials (823), and in the other two trials (826, 827) patients were rerandomized to placebo or active drug in a cross-over design. The percentage of patients losing more than 5% ranged from 23% to 49.2% in the placebo-treated group and 49% to 68.5% in those

TABLE 16. Effect of orlistat in clinical trials of 1 and 2 yr in duration

Author	Year	No. subjects		Dose (mg/tid)	Duration of study (wk)	Run In (wk)	Diet	Initial wt. (kg)		Wt loss (kg or %)		Met Criteria		Comments
		Placebo	Drug					Placebo	Drug	FDA	CPMP			
Drent (123a)	1993	19	20	50 tid	12	4	500 kcal/day deficit	81.9	85.5	-2.1 kg	-4.3 kg	No	No	Single site
Drent <i>et al.</i> (821)	1995	46	48	30 tid	12	4	500 kcal/day deficit	90.0	92.1	-2.98 kg	-3.61 kg	No	No	Multicenter
			45	60 tid					92.6		-3.69 kg	No	No	Dose-ranging
			47	120 tid					94.1		-4.74 kg	No	No	
Drent and van der Veen (828)	1995	7	7	120 tid	12	4	500 kcal/day deficit	86.8	89.8	-2.8 kg	-4.2 kg	No	No	Substudy of 821
James <i>et al.</i> (822)	1997	23	23	120 tid	52	4	600 kcal/day deficit	99	100	-2.6 kg	-8.4 kg	Yes	No	Wt loss at 12 mo
Finer (824)	1997	108	110		52	4	600 kcal/day deficit	98.4	97.9	-2.6 kg	-8.4 kg	No	No	British 1 yr
Van Gaal <i>et al.</i> (825)	1998	125	122	30 tid	24	4	500 kcal/day deficit	35 BMI	35	-6.5%	-8.5%	No	No	Multicenter
			124	60 tid					34		-8.8%	No	No	Dose-ranging
			122	120 tid					35		-9.8%	No	±	
			120	240 tid					34		-9.3%	No	±	
Sjostrom <i>et al.</i> (826)	1998	340	343	120 tid	104	4	600 kcal/day deficit (yr 1)	99.8	99.1	-6.1 kg	-10.3 kg	No	No	European multicenter
Hollander <i>et al.</i> (829)	1998	159	162	120 tid	52	5	maintenance (yr 2)	99.7	99.6	-6.1%	-10.2%	No	Yes	Cross-over 52 wk data
Davidson <i>et al.</i> (827)	1999	223	657	120 tid	104	4	500 kcal/day deficit 30% fat (yr 1)	100.6	100.7	-4.3 kg	-6.2%	No	No	US diabetic study
				120 tid			600 kcal/day deficit (yr 1)			-5.8 kg	-8.8 kg	No	No	US Multicenter cross-over 52-wk data
							Maintenance (yr 2) 30% fat			-5.8%	-8.7%			

tid, Three times per day.

treated with orlistat. Using a criterion of greater than 10% weight loss, 17.7% to 25% of placebo-treated patients reached this goal compared with the more successful 38.8% to 43% among those treated with orlistat. Nearly two-thirds of the enrolled patients completed year 1.

Data on the second year of treatment are available from three studies. In one study (823) subjects remained on the same treatment for 2 yr. At the end of the second year, weight loss from baseline was  $-7.6\% \pm 7.0\%$  for those on orlistat compared with  $-4.5\% \pm 7.6\%$  in the placebo group. At 1 yr the corresponding losses were  $-9.7 \pm 6.3\%$  and  $-6.6 \pm 6.8\%$ . In the two other studies, the orlistat subjects were rerandomized at the end of 1 yr to placebo or orlistat 60 or 120 mg three times a day (822, 827). One of these is shown in Fig. 17 (826). Those remaining on orlistat for 2 yr regained 32.5% from the end of year 1 to the end of year 2 but were still  $-8.8 \pm 7.6\%$  below baseline. The patients who continued on orlistat with the maintenance diet regained half as much (2.5 kg or 2.6%) as those switched from orlistat to placebo (5.7 kg or 52% regain). In this trial subjects who received orlistat in the second year and placebo in the first lost an average of 0.9 kg more. These data show that initial weight loss is greater and that weight regain is slowed by orlistat. The 2-yr US Prevention of Weight Regain Study treated patients with orlistat 30, 60, or 120 mg three times a day, who had lost more than 8% of their initial weight by dieting (830). At the end of 1 yr the placebo-treated group had regained 56% of the weight they had lost, in contrast with a regain of 32.4% in the group treated with orlistat 120 mg three times a day.

Orlistat improves some serum lipid values more than can be explained with weight reduction alone (812, 826, 831). In a multicenter trial, Tonstad *et al.* (831) compared orlistat at 30–360 mg/day with placebo on a weight-maintaining diet in an 8-wk double-blind, randomized trial. Total cholesterol and LDL cholesterol were reduced 4–11% and 5–10%, respectively, in the orlistat groups compared with placebo (831). This reduction is probably related to the fecal fat loss induced by the drug, and this loss may necessitate supplementation with fat-soluble vitamins during treatment. During the weight loss period there was a decline in total cho-

lesterol, LDL cholesterol, HDL cholesterol, fasting glucose, and blood pressure. Reitsma *et al.* (831) reported that postprandial lipemia was reduced. Orlistat appears to reduce cholesterol but not glucose or blood pressure by more than can be accounted for by the decrease in body weight.

In a 1-yr trial in diabetics (829), the orlistat-treated patients lost 6.2% and the placebo-treated patients lost 4.3% of their initial weight (Table 16). There was also a reduction in the need for hypoglycemic medication.

*c. Side effects.* The side effects with orlistat are to be expected from its mechanism of action on pancreatic lipase (832, 833) (Table 17). These include intestinal borborygmi, flatus, and abdominal cramps. The most troubling were fecal incontinence, oily spotting, and flatus with discharge. In a comparison of pooled data on 1,740 placebo-treated and 2,038 orlistat-treated patients, orlistat appeared to be well tolerated with the principal complaints being GI symptoms. Most were mild and occurred within the first few weeks (832). More placebo-treated patients (35%) withdrew prema-

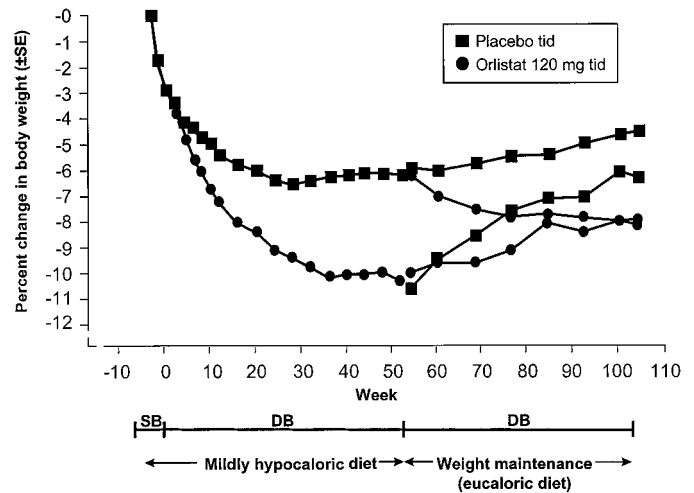


FIG. 17. Orlistat and body weight. [Adapted with permission from L. Sjöström *et al.*: *Lancet* 352:167–172, 1998 (826). © The Lancet Ltd.]

FIG. 16. A possible model of hypothalamic feeding (DRN, dorsal Raphe nucleus; URO, urocortin; 5-HT, serotonin; ARC, arcuate complex; LC, locus coeruleus; NPY, neuropeptide Y; NE, nor-epinephrine; MC-4, melanocortin-4 receptor; PVN, paraventricular nucleus; CRHBP, CRH binding protein; ORX, orexin R; AGRP, agouti-related protein; VMN, ventromedial nucleus; SNS, sympathetic nervous system; MCH, melanin concentrating hormone; MPG, motor pattern generator; DMV, dorsal motor nucleus of the vagus).

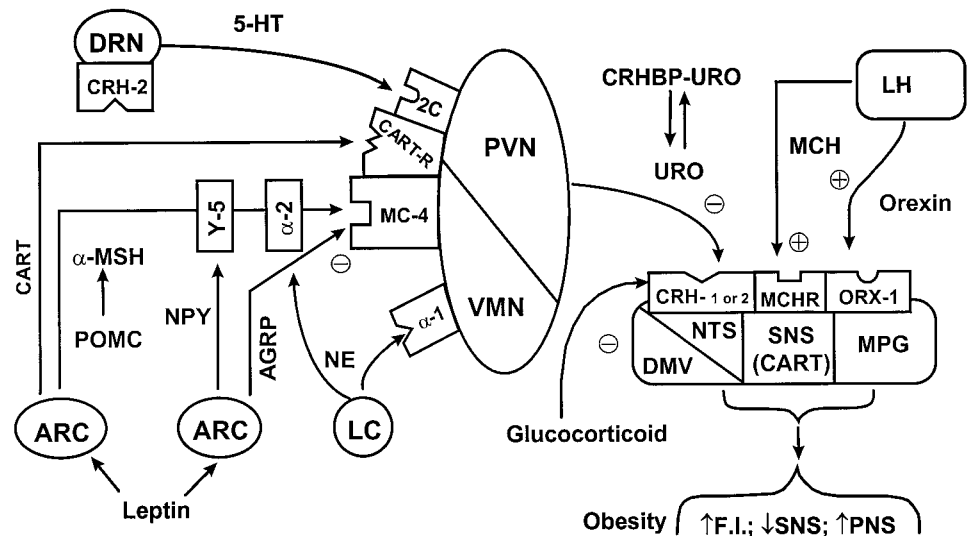


TABLE 17. Percentage of gastrointestinal symptoms reported by placebo and orlistat-treated patients at 1 and 2 yrs of treatment

	Year 1 (%)			Year 2 (%)		
	Placebo	Orlistat	Withdrawal	Placebo	Orlistat	Withdrawal
Oily spotting	1	27	1.7	0.2	4	0.2
Flatus and discharge	1	24	0.6	0.2	2	0.2
Fecal urgency	7	22	0.3	2.0	3	0.0
Fatty/oily stool	3	20	0.1	1.0	6	0.3
Oily evacuation	1	12	0.0	0.2	2	0.0
Increased defecation	4	11	0.3	1.0	3	0.0
Fecal incontinence	1	8	1.1	0.2	2	0.2

Derived from Ref. 832.

turely than orlistat-treated patients (29%). There was no evidence for gallstones, renal stones, or cardiovascular or CNS events. Hill et al (820) evaluated orlistat in a 12-month trial of weight maintenance. Initially, 1,313 patients were enrolled in a dietary weight loss program, and the 729 subjects who lost more than 8% of initial body weight were randomized to placebo or 90, 180, or 360 mg of orlistat in three divided doses daily for 52 weeks. The percentage weight regain was significantly less in the group treated with 360 mg of orlistat (32.4% regain from nadir) than for the placebo (56.0%), 90 mg (53.3%), or 180 mg of orlistat (47.2%) daily.

**2. Amylase inhibitors.** Obese individuals have impaired starch tolerance due to their insulin resistance. Berchtold and Kieselbach (835) reported that an amylase inhibitor, BAY e 4609, improved insulin and glucose during a starch tolerance test but did not cause weight loss in a controlled trial of 59 obese humans. Nevertheless, commercial preparations of amylase inhibitors were sold in the early 1980s with the claim that taken in tablet form 10 min before meals would block the digestion of 100 g of starch in the diet. Garrow *et al.* (836) tested this claim with starch enriched with carbon 13 and found that these "starch blockers" do not effect starch digestion or absorption *in vivo*.

In 1979 Hillebrand *et al.* (837, 838) reported that acarbose (Bayer Corp., West Haven, CT), an  $\alpha$ -glucosidase inhibitor, reduced the insulin and glucose response to a mixed meal. Puls *et al.* (839) reported a dose-related inhibition of weight gain in both Wistar and Zucker rats. Similar findings and a reduction in visceral adipose tissue were demonstrated with another  $\alpha$ -glucosidase inhibitor, AO-128, suggesting that these effects are related to this class of compounds (840, 842). William-Olsson (843) treated 24 weight-reduced women with acarbose and inhibited weight regain. Wolever *et al.* (844) have recently reported a 1-yr double-blind, randomized, placebo-controlled study in 354 Type II diabetic subjects. Subjects on acarbose lost 0.46 kg while the placebo group gained 0.33 kg, which was statistically significantly different ( $P = 0.027$ ) (844).

We conclude that  $\alpha$ -amylase inhibitors have no place in the treatment of obesity. Acarbose gives only a small weight loss and will never be indicated as an obesity treatment, but it certainly deserves consideration in treating obese Type II diabetic subjects who have failed treatment with diet and exercise.

**3. Olestra.** Acylation of sucrose with five or more fatty acids produces a molecule that has the physical characteristics of triglyceride but which cannot be digested by pancreatic lipase. Olestra (Olean) is a commercially available (Procter &

Gamble, Cincinnati, OH) form of sucrose polyester that is largely solid at body temperature. This fat substitute cannot be digested and is currently being used to cook snack foods. Short-term studies substituting olestra for triglyceride in the diet show two patterns of adaptation. When olestra (sucrose polyester) was substituted in a single breakfast meal, there was energy compensation over the next 24–36 h in healthy young males (845, 846). Substitution with olestra at the noon or evening meal lowered digestible fat from 40% to 30%, and there was no energy or nutrient compensation over the next 24 h (847). However, when the olestra substitution lowered the fat intake from 30% to nearly 20% of energy over three meals, healthy subjects felt less satisfied at the end of the substitution and compensated for nearly 75% of the energy deficit over the next day (848).

In longer-term experiments, lasting 2 wk or 3 months, the substitution of olestra for one-third of the fat in a 40% fat diet reduced energy consumption by about 15% (2,000 kcal reduced to 1,750 kcal) for the same weight of food. In each experiment there was only a partial compensation, suggesting that when the energy density of the diet changed, the subjects continued to eat for the same mass of food, even though it provided fewer metabolizable calories. Weight loss in the 2-wk experiment was 1.5 kg and in the 3-month experiment was more than 5 kg, which was significantly greater than the control group (849, 850).

#### B. Postabsorptive modifiers of nutrient metabolism

**1. GH.** Human GH is a 191-amino acid peptide composed of a single chain with two disulfide bonds (851). It is of interest in relation to obesity because obese individuals secrete less GH (852), because GH enhances lipolysis (853) and because it increases metabolic rate and leads to changes in fat patterning in hypopituitary children treated with GH (854). Based on these observations, early studies with GH showed that it would enhance mobilization of fat, stimulate oxygen consumption (855), and lead to reduced protein loss in obese people (856). When given to fasting obese subjects on a metabolic ward, it accelerated ketosis by increasing fatty acid mobilization (857). More recently, treatment of adult GH deficiency has been shown to reduce body fat (858), whereas treatment of acromegaly in which GH secretion is high increases fat (859).

The nitrogen-sparing effects of GH in human subjects on a reduced-calorie diet were investigated in a series of studies using different levels of caloric restriction (860–867). In all of these studies, GH increased the concentration of FFA in the

circulation, increased insulin-like growth factor I, and increased insulin and C-peptide. In most studies it preserved nitrogen and increased fat loss or the loss of fat relative to body weight loss. Table 18 summarizes these data and other clinical trials in obese subjects. Most of the studies have been relatively short term with treatment lasting from 21 days to 5 wk (Table 18) (856, 862, 866), but a few have lasted from 11–39 wk (860, 861, 868–870). Most of the subjects were women. Metabolic rate is increased where measured, and respiratory exchange rate is reduced, indicating that more fat is being burned. Insulin-like growth factor I increased FFA and the rate of fat loss relative to protein loss increased. A number of side effects were noted (866) that reduce the enthusiasm for long-term trials. The only long-term study lasted 9 months and used continuous daily injections of GH. There were 15 men in each arm of the randomized double-blind placebo-controlled clinical trial (868). In these men, GH enhanced fat loss with a larger percentage of this fat coming from the visceral than from the subcutaneous compartment (Table 18).

**2. Metformin.** Metformin is a biguanide that is approved for the treatment of diabetes mellitus, a disease that is exacerbated by obesity and weight gain. Although the cellular mechanism for the effects of metformin are poorly understood, it has three effects at the clinical level (869–876). First, it reduces hepatic glucose production, which is a major source of circulating glucose. Metformin also reduces intestinal absorption of glucose, which is a second source of circulating glucose. Finally, metformin increases the sensitivity to insulin, thus increasing peripheral glucose uptake and utilization.

Metformin has been associated with significant weight loss when compared with sulfonylureas or placebo (Table 19). Campbell *et al.* (873) compared metformin and glipizide (Mylan, Morgantown, WV) in a randomized double-blind study of Type II diabetic individuals who had failed on diet. The 24 subjects receiving metformin lost weight and had better diabetic control of fasting glucose and glycohemoglobin than did the glipizide group. The glipizide group gained weight and the difference in weight between the two groups at the end of the study was highly significant. In a double-blind placebo-controlled trial in subjects with the insulin resistance syndrome, metformin also increased weight loss. Fontbonne *et al.* (874) reported the results from the BIGPRO study, a 1-yr French multicenter study that compared metformin with placebo in 324 middle-aged subjects with upper body obesity and the insulin resistance syndrome. The subjects on metformin lost significantly more weight (1–2 kg) than the placebo group, and the study concluded that metformin may have a role in the primary prevention of Type II diabetes mellitus. The package insert for metformin (875) describes a 29-wk double-blind study comparing glyburide (Novopharm USA, Schaumburg, IL) 20 mg/day with metformin 2.5 g/day and their combination in 632 Type II diabetic subjects who had inadequate glucose control. The metformin group lost 3.8 kg compared with a loss of 0.3 kg in the glyburide group and a gain of 0.4 kg in the combined group. The package insert also described a double-blind controlled study in poorly controlled Type II diabetic sub-

jects comparing metformin 2.5 m/day to placebo. Weight loss in the placebo group was 1.1 kg, compared with 0.64 kg in the metformin group. Lee and Morley (876), however, compared 48 Type II diabetic women in a double-blind controlled trial randomizing subjects to metformin 850 mg twice a day or a placebo. Metformin-treated subjects lost 8.8 kg over 24 wk compared with only 1.0 kg in the placebo group, a highly significant difference ( $P < 0.001$ ). Although metformin may not give enough weight loss to receive an indication from the USFDA for treating obesity, it certainly deserves consideration in obese Type II diabetic individuals who have failed diet and exercise treatment for their diabetes, and it has been used in children (877).

**3. Pyruvate.** Three clinical trials suggest that pyruvate or its metabolites affect body weight. In seven obese subjects on a metabolic ward (878), addition of pyruvate at 13% of dietary calories in a 1,000 calorie diet produced a  $5.9 \pm 0.7$  kg body weight loss and a  $4.0 \pm 0.5$  kg of body fat loss compared with a  $4.3 \pm .3$  kg weight loss and  $2.7 \pm .2$  kg body fat in seven obese women who had polycose substituted for pyruvate in equicaloric amounts in a 21-day study. In a second metabolic ward study (879), 13 obese women were randomized to a 500-calorie diet containing 20% of calories as a 1:1 mixture of dihydroxyacetone and pyruvate or a 500-calorie diet in which the pyruvate and dihydroxyacetone were replaced by polycose. Subjects receiving the pyruvate lost  $6.5 \pm 0.3$  kg of body weight and  $4.3 \pm 0.2$  kg of body fat compared with  $5.3 \pm 0.2$  kg of body weight and  $3.5 \pm 0.1$  kg of body fat on the polycose-supplemented diet ( $P < 0.05$ ). Nitrogen balance and leucine metabolism were not different. In a third study carried out on a metabolic ward (880), 17 obese women were treated with a 300-calorie diet for 21 days and lost 9.1 kg (20 lb). The women were then randomized to receive a balanced diet for the next 21 days with an energy content of 1.5 times their BMR with 15% of dietary calories coming from polycose or dihydroxyacetone and pyruvate in a 3:1 ratio. The group with the triose-supplemented diet gained less weight (4.9 kg *vs.* 0.7 kg,  $P < 0.01$ ) and less fat (4.1 kg *vs.* 1.1 kg  $P < 0.01$ ) than the polycose-supplemented group. Nitrogen balance was not different between the two groups. These clinical studies again suggest that glucose metabolites and their derivatives may be worthwhile targets for weight loss drugs.

**4. Hydroxycitrate.** (–)-Hydroxycitrate inhibits citrate lyase, the first extramitochondrial step in fatty acid synthesis from glucose. This compound causes weight loss by decreasing calorie intake (881). Although the mechanism of this inhibition of food intake is not clear, studies by Hellerstein and Xie (882) suggest that it may be through trioses like pyruvate. In a double-blind trial of 60 subjects who were randomized to hydroxycitric acid 1,320 mg/day or placebo and a 1,200-calorie diet for 8 wk, the hydroxycitrate group lost 6.4 kg whereas the placebo group lost only 3.8 kg ( $P < 0.001$ ) (883). *Garcinia cambogia*, an herbal product containing hydroxycitrate, has been compared with placebo in a double-blind randomized clinical trial (884). The herbal product was given three times a day in a dose to provide 500 mg each time. The subjects treated with hydroxycitrate lost no more weight than those given placebo.



TABLE 18. Clinical studies with GH in obesity

Author	Year	No. of subjects		Dose of medication	Duration (wk)	Diet	Weight loss (kg)		Fat loss (kg or %)		Comments
		P	D				P	D	P	D	
Bray <i>et al.</i> (856)	1971	4F (hGH-n = 2) (hGH + T <sub>3</sub> n = 4)		5 mg/day	hGH alone, 30 day hGH + T <sub>3</sub> , 15 day	900 kcal/day Formula diet	211 g/day 523 g/day 550 g/day T <sub>3</sub>	337 g/day 240 g/day 380 g/day T <sub>3</sub> +hGH			Metabolic ward
Clemmons <i>et al.</i> (860)	1987	5F 3M		0.1 mg/kg IBW every other day wk 3-5 wk 8-10	11 wk	24 kcal/kg IBW 1.0 prot/kg IBW	-4.16	-3.42	-2.64 ± 1.08	-3.06 ± 1.39	Metabolic ward Cross-over study or IGFI ↑ Nitrogen balance im- proved
Snyder <i>et al.</i> (861)	1988	8F 2M	8F 2M	0.1 mg/kg IBW every other day wk 2-12	13 wk	18 kcal/kg IBW 1.2 g prot/kg IBW	-15.2 ± 3.8	-13.9 ± 3.0	-7.5 ± 1.5%	-8.1 ± 2.4%	Metabolic ward Parallel arm study; Nitrogen balance posi- tive but less with time IGF-1 ↑ FFA ↑
Snyder and Clemmons (862)	1989	11F		0.1 mg/kg IBW every other day wk 2-4	Two 5-wk periods 5-wk washout	12 kg kcal/kg IBW 1.0 g prot/kg IBW Diet I, 72% Carb Diet II, 20% Carb	-8.5 ± 1.7 -8.2 ± 0.7	-7.4 ± 1.9 -7.5 ± 1.8	-2.8 ± 0.7%	-3.7 ± 1.0% -3.8 ± 0.9% -3.6 ± 1.2%	Metabolic unit study; GH ↑ fat loss as % wt loss from 64% to 81%
Snyder <i>et al.</i> (863)	1990	8F		0.1 mg/kg daily	Two 5-wk periods 5-wk washout	12 kcal/kg IBW	-7.2 ± 2.3	-6.3 ± 5.0	-3.6 ± 1.1%	-3.5 ± 1.1%	Cross-over; improved N <sub>2</sub> balance ↑ IGF-I
Richelson <i>et al.</i> (864)	1994	9 F Premeno- pausal		0.03 mg/kg IBW/ day	Two 5-wk periods 5-wk washout	Not specified		+8.0 ± .13		-2.1 ± .06 kg	Cross-over; visceral fat LPL ↓; FFA ↑; C-pep- tide ↑
Jorgensen <i>et al.</i> (865)	1994	10 F Premeno- pausal		0.03 mg/kg IBW/ day	Two 5-wk periods 5-wk washout	Not specified	Data not given Subjects may overlap with paper above		Data not given Subjects may overlap with paper above		Cross-over T <sub>3</sub> ↑; EE ↑; FFA ↑; RER ↓; IGF-I ↑
Snyder <i>et al.</i> (866)	1995	11		0.05 mg/kg	4 wk	15 kcal/kg	-8.4 ± 1.4	-7.3 ± 1.4	-2.6 ± 1.0%	-3.4 ± 0.9%	Cross-over IGF-I ↑
Drent <i>et al.</i> (867)	1995	6 F 2 M	7 F	6 μ/day	8 wk	VLCD + exercise	-12.8 ± 5.0	-13.8 ± 4.0			IGF-I ↑ IGFBP-3 ↑
Johannsson <i>et al.</i> (868)	1997	15 M 15 M	15 M	9.5 μg/kg daily	39 wk	Not specified	+0.7	FFM		-9.2 ± 2.4%	Parallel arm
Karlsson <i>et al.</i> (869)	1998	15 M 15 M	15 M	9.5 μg/kg daily	39 wk	Not specified	+0.5	-1.0	-0.1 kg	-3.0 kg	Parallel arm Same patients as in Ref. 868 BMR ↑; leptin ↓; vis- ceral fat ↓ 68.1%
Thompson <i>et al.</i> (870)	1998	7	9	GH 0.025 mg/kg BW/day	12 wk	500 kcal/day deficit	-3.7	-4.2	-3.5	-6.3 kg	Parallel arm
			9	IGH 0.015 mg/kg/ day				-3.5		-4.0 kg	
			10	GH + IGFI				-5.6		-8.4 kg	

P, Placebo; D, drug; VLCD, very-low calorie diet; prot, protein; Carb, carbohydrate; M, male; F, female; IBW, ideal body weight.

TABLE 19. Clinical trials with metformin for the treatment of obese diabetics

Author	Year	Duration	No. subjects drug/control	Control	Subjects	Design	Wt. loss (kg)		Wt. loss (%)		Comment
							Placebo	Drug	Placebo	Drug	
McAlpine <i>et al.</i> (871)	1988	6 months 3 mo/3 mo	21 of 27 completed	Gliclazide	Obese type II diabetics	Open-label crossover	-1.4 kg	-1.0 kg			
Josephkuttly and Potter (872)	1990	6 months 3 mo/3 mo	20	Tolbutamide	Type II diabetes	Double-blind random crossover	-1.6 kg	-2.0 kg			
Campbell <i>et al.</i> (873)	1994	1 yr	24/24	Glipizide	Diet failed type II diabetes	Open-label, random, parallel, controlled	-2.62 kg	-1.97 kg			
Fontbonne <i>et al.</i> (874)	1996	1 yr	162/162	Placebo	Upper body obesity	Double-blind random, placebo-controlled	0.8 kg	2.0 kg			
Scheen <i>et al.</i> (875)	1995	29 wk	210/209 (Gly)/213 (comb.)	Glyburide with and without metformin	Type II diabetes uncontrolled on maximal glyburide	Double-blind random comparison	0.3 kg (glyburide) -0.4 kg (combined)	3.8 kg			
Lee and Morley (876)	1998	24 wk	24/24 × 16/16	Placebo	Obese type II diet-controlled diabetics	Double-blind random parallel placebo vs. 85 mg bid	1.0 kg 0.9 kg	8.8 kg 7.8 kg			$P < 0.001$ difference in weight loss

Gly, Glyburide; comb., combination.

5. *Chromium picolinate*. Chromium picolinate has received notoriety as a dietary supplement for weight loss based on animal studies. Page *et al.* (885) reported an increased percentage of muscle and a decreased percentage of fat in swine supplemented with chromium picolinate during a time when weight increased from 55 kg to 119 kg. These findings were confirmed by Mooney and Cromwell (886) and by Lindemann *et al.* (887), who demonstrated an increased litter size in reproducing sows as well. Although the animal literature is encouraging, the studies in humans have not confirmed the experience in swine. Hasten *et al.* (888) studied the effect of 200  $\mu\text{g}/\text{day}$  of chromium picolinate compared with placebo in a randomized double-blind trial lasting 12 wk during weight training. The only significant difference was a greater increase in body weight in the females supplemented with chromium picolinate (888). This and several other studies show no effect of chromium picolinate on body composition in humans (889–891).

6. *Human CG (hCG)*. Injection of small doses of hCG daily for 6 wk or more has been widely used in the treatment of obesity after the introduction of this treatment for undescended testes and its use with alleged success in patients with what was termed “Frohlich’s” syndrome. A number of controlled clinical trials have been done to evaluate the use of hCG, and these have recently been reviewed (892, 893) (Table 20). Lijesen *et al.* (892) evaluated 16 uncontrolled and 8 controlled studies found through a literature search. All studies were graded on a 100-point scale, and those making a score of 50 or greater were evaluated. Of these studies only one concluded that hCG was a useful adjunct to a weight loss program compared with a placebo. Table 20 is a summary of the double-blind placebo-controlled randomized trials that have been published in the past 25 yr (894–903). We conclude that hCG is no more effective than placebo, but we also note that all of these studies used a very-low-calorie diet that gave a significant weight loss in both groups.

7. *Androgens*. For this discussion, androgens will be divided into two groups, the “weak” androgenic compounds including androsterone, dehydroepiandrosterone,  $\Delta^4$ -androstenedione, and anabolic steroids, and the potent androgens, testosterone and dihydrotestosterone (DHT).

a. *Dehydroepiandrosterone*. Dehydroepiandrosterone (DHEA =  $\Delta^5$ -androstene-3- $\beta$ -hydroxy-17-one) is a product of the adrenal gland. In human beings, this steroid and its sulfated derivative are the most abundant steroids produced by the adrenal. In experimental animals the quantities are much lower and in rodents are just above the threshold for detection. In spite of their high concentration in the circulation and abundance as adrenal products, no clear function has been identified. DHEA levels decline with age in men and women (186). With very high BMI values of 40–60 kg/m<sup>2</sup>, on the other hand, there was a significant negative correlation. In contrast with the limited effect, relationship between DHEA and body weight or total fat, there is a clearer relation with fat distribution (904) and hyperinsulinemia (186). Animal studies have shown that DHEA may be immunosuppressive and have antiatherogenic and antitumor effects (185). Because mice, rats, cats, and dogs fed DHEA

TABLE 20. Clinical trials with hCG injections for the treatment of obesity

Author	Year	No. of subjects		Diet (kcal/day)	Design	Wt. loss (kg)		Wt. loss (%)		Comments								
		Placebo	Drug			Placebo	Drug	Placebo	Drug									
Carne (894)	1961	12/10 11/8 10/7	13/12	500	Diet + hCG Diet + vehicle Diet + vehicle Diet only	-8.6 -10.1 -8.0	-9.5	-10.3 -12.2 -11.3	-12.5	Injections were better than no injections, but hCG not better than saline.								
											Craig <i>et al.</i> (895)	1963	11/9	550	Randomized double-blind	-3.0	-4.0	hCG had no demonstrable effect. Weight loss due to diet.
Asher and Harper (898)	1973	20/13	500	Modified double-blind (3 patients from each vial)	-9.0	-5.0	-6.8	-11.5	hCG possibly effective. Five of placebo group and none of hCG group received fewer than 21 injections.									
										Stein <i>et al.</i> (899)	1976	26/21	500	Double-blind, randomized, placebo-controlled	-7.0	-7.2	-9.3	-9.5
Greenway and Bray (893)	1977	20/20	500	Double-blind, randomized, placebo-controlled	-8.1	-8.8	-10.2	-10.9	No difference in weight loss, hunger rating, mood or body circumference between hCG and placebo.									
										Shetty and Kalkhoff (900)	1977	5/5	6/6	500	Double-blind in patient study lasting 30 days	-9.4	-9.3	-9.5
Bosch <i>et al.</i> (901)	1990	20/16	20/17	1190 (5000 kJ)	Double-blind, randomized	-4.6	-3.2	-4.9	-3.4									

have lost weight, it has been evaluated as a potential treatment for obesity. A recent structure function analysis by Lardy *et al.* (187) showed that the biological effect on body fat of DHEA-related steroids was greatest with 7-oxo-DHEA derivatives.

Several clinical studies with DHEA have been done and are reviewed by Clore (185). In a study lasting 28 days with 10 normal weight volunteers, DHEA at 1,600 mg/day, near the limit where hepatic toxicity is a risk, had no effect on body weight or on insulin sensitivity as assessed by the euglycemic-hyperinsulinemic clamp (906). A similar study showed no effect of DHEA on energy expenditure, body composition, or protein turnover (907). After 28 days of treatment with DHEA, obese male volunteers showed no improvement in body fat or insulin sensitivity (908). In obese female volunteers there was likewise no change in body fat, but there was a decrease in insulin sensitivity (909). Based on these negative studies in both lean and obese human subjects, it would appear that DHEA is ineffective in human obesity. A steroid derivative of DHEA called etiocholanedione has been suggested to reduce body weight in one preliminary study (910). More data are awaited.

*b. Testosterone and DHT.* Testosterone is the principal product of the testis and is responsible for masculinization. Testosterone is converted to DHT in peripheral androgenic tissues and converts the "soft" hair to the terminal hair in male androgenic areas. Testosterone can also be produced by the adrenal, the ovary, and by conversion in peripheral tissues (911). In females, 25% of testosterone comes from the ovary, 25% from the adrenal, and 50% from peripheral conversion. In human subjects, the concentration of testosterone is positively related to the level of visceral fat in women and negatively correlated with visceral fat in men (912, 913). A recent report suggests that androstane-3 $\alpha$ -17 $\beta$ -diol may be a correlate of visceral obesity (914).

The inverse relationship between testosterone and visceral fat in men suggested the possibility that visceral fat might be reduced by treatment with testosterone. Marin *et al.* (915–917) evaluated this in two trials using men with low-normal circulating testosterone levels (<20 nmol/liter) and a BMI greater than 25 kg/m<sup>2</sup>. In the first trial, testosterone 80 mg twice daily was given orally as the undecenoate. The 11 men who received testosterone had a significant decrease of visceral fat mass as measured by computed tomography compared with the 12 men who received placebo for 8 months. There were no changes in body mass, subcutaneous fat mass, or lean body mass. Insulin sensitivity was improved (915).

In a second trial by Marin *et al.* (916), 31 men were randomly allocated to three groups receiving either placebo, testosterone, or DHT. The testosterone was given as a gel with 5 g containing 125 mg of testosterone applied to the arms daily. The DHT was applied in a similar gel at the same dose. The placebo group received only the gel. After 9 months, the testosterone-treated group showed a significant decrease in waist circumference and visceral fat. The DHT-treated group, on the other hand, showed an increase in visceral fat. Testosterone was increased in the group treated with the testosterone. Treatment with DHT reduced testos-

terone and increased DHT levels. Insulin sensitivity was also improved by treatment with testosterone (916, 917).

Two additional studies have examined the effects of anabolic steroids in men and women (918, 919). The first was a 9-month trial on 30 healthy overweight men with mean BMI values of 33.8–34.5 kg/m<sup>2</sup> and testosterone values between 2 and 5 ng/ml (919). During the first 3 months when an oral anabolic steroid (oxandrolone) was given daily, there was a significantly greater decrease in subcutaneous fat and a greater fall in visceral fat than in the groups treated with placebo or testosterone enanthate injected every 2 wk. Because of the drop in HDL cholesterol, which is a known side effect of oral anabolic steroids, the anabolic steroid group was changed to an injectable drug, nandrolone decanoate. The effects were similar to those of testosterone enanthate. The data with testosterone given as a biweekly injection did not replicate the data of Marin *et al.* (915, 916), and the biweekly injections of nandrolone failed to maintain the difference seen with daily treatment with oxandrolone. This suggests that to obtain the visceral effects with steroids, frequent if not daily administration may be needed.

In a second 9-month trial with 30 postmenopausal overweight women, Lovejoy *et al.* (919) randomized subjects to nandrolone decanoate, spironolactone, or placebo. The weight loss was comparable in all three groups, but the women treated with nandrolone decanoate gained lean mass and visceral fat and lost more total body fat. Women treated with the antiandrogen, spironolactone, lost significantly more visceral fat. The conclusion from the four studies described above is that visceral and total body fat can be manipulated separately, and that testosterone plays an important role in this differential fat distribution in both men and women.

## V. Drugs That Increase Energy Expenditure

Thermogenesis is the third mechanism for development of drugs to treat obesity. Thyroid hormone is the prototypical agent in this class. Because of its many other effects it is not useful to treat obesity.  $\beta$ -Adrenergic agonists are another approach to using thermogenesis to treat obesity. Ephedrine and caffeine combined have been shown to be more effective in a 6-month clinical trial compared with placebo. Synthetic  $\beta$ -adrenergic agonists developed against rodent receptors have not proven very effective. Drugs designed against the human receptor are awaited.

### A. Thyroid hormone

The active substance from the thyroid was extracted more than 100 yr ago and was reportedly used for the treatment of obesity in 1893 (9). Subsequently T<sub>4</sub> was isolated and structurally identified. T<sub>4</sub> is the principal iodinated compound in the thyroid gland and is secreted into the circulation where it is avidly bound to a binding globulin and slowly turned over. The discovery of T<sub>3</sub> in 1953 was followed by the recognition that the principal source of this active form of thyroid hormone is through peripheral conversion from T<sub>4</sub> to T<sub>3</sub> by 5'-deiodinase. This enzyme is active in a number of

tissues and is under control of the sympathetic nervous system in brown adipose tissue (920).

When studies early in this century suggested that obese individuals had a "low metabolic rate," thyroid extract became a popular way to treat obesity. With the introduction of newer systems for indirect calorimetry, the metabolic rate of obese individuals was shown to have a linear relationship to their fat free mass (FFM). In obese individuals the FFM and metabolic rate are related. Similarly, sophisticated techniques for evaluating thyroid hormonal status in obesity showed normal TSH, normal  $T_4$ , but a suggestive increase in  $T_3$  with increasing body weight (921, 922). This may well be due to nutritional status, since the level of  $T_3$  rises with overfeeding (923) and falls with starvation (924, 925) or with low-carbohydrate diets (926).

Clinical studies have used thyroid,  $T_4$ , and  $T_3$ . Most were conducted in metabolic wards (922, 926–928, 934, 935) and were often open-label studies (929–931, 934). Ball *et al.* (926) showed that four obese patients on a metabolic ward lost more lean body mass with a diet plus large doses of desiccated thyroid than with the diet alone, and they showed that the changes in myxedematous patients were similar to those in the obese (928). Of note is that the negative nitrogen balance produced by thyroid hormone reached its peak early in treatment and then moved slowly toward balance. Similar findings have been reported in normal subjects given small amounts of  $T_3$  (932). When the increase in energy expenditure produced by thyroid hormone is partitioned between catabolism of protein and fat, oxidation of fat appears to provide nearly 75% of the energy, and protein supplies 25% of the energy, but the loss of lean tissue accounts for 75% of the weight loss (922) due to its large water content (low energy content). In subjects eating a very-low-calorie diet, Sabeh *et al.* (933) found that desiccated thyroid increased weight loss by almost 40%. In another metabolic ward study, Wilson and Lamberts (934) added 25  $\mu\text{g}$  of  $T_3$ , three times a day, to a 320 kcal/day diet and observed that the mean daily weight loss increased from  $269 \pm 27$  g/day to  $395 \pm 32$  g/day while N balance did not change. The issue of increased protein loss arises repeatedly in these studies. Lamki *et al.* (935) addressed this issue by comparing a 600 kcal/day diet and 0.3 mg/day of thyroid with a 1,200 kcal/day diet with 0.9 mg/day of thyroid each administered over periods of 20–30 days. Before admission to the metabolic unit, each of the four patients had been treated with 0.3 mg/day of  $L-T_4$  and were weight stable, weighing 130–167 kg. During the 60- to 78-day periods on the metabolic ward they lost between 30 and 35 kg. The overall mean of the nitrogen balance was 4.09 g N lost/day for the period with 600 kcal/day and 0.3 mg/day of  $T_4$  and 3.45 g N lost/day for the 1,200 kcal/day + 0.9 mg/day of  $T_4$ .

Desiccated thyroid extract,  $T_4$ , and  $T_3$  have all been used in clinical trials. The early work using relatively low doses of desiccated thyroid did not find any advantage to the addition of thyroid to a weight reduction program compared with diet (936, 937). Kaplan and Jose (938) used desiccated thyroid with and without *d*-amphetamine in a study of 53 patients on amphetamine who were matched to 48 patients treated with the combination of  $T_4$  and *d*-amphetamine. After 12 wk of treatment, the amphetamine-treated patients had lost 4.1 kg

(4.9%) and the group treated with *d*-amphetamine and thyroid had lost 6.6 kg (7.7%). Danowski *et al.* (930) treated 66 patients with diet only and 29 with diet and thyroid (mean dosage 9 grains/day) for periods of 4–41 months. Mean initial weight was 97 kg in the diet group and 96 kg in the thyroid-treated group. Of the diet group, only 12% lost more than 13.6 kg (30 pounds) compared with 38% in the thyroid-treated group.

$T_3$  has largely replaced thyroid and  $T_4$  in recent studies as well as some older ones. Gelvin *et al.* (939) was one of the first to use  $T_3$  in a controlled study. The 57 patients who completed the study had received instruction in a 1,000 kcal/day diet and received amphetamine 10 mg with amobarbital 65 mg for 8 wk or amphetamine-amobarbital plus an increasing dose of  $T_3$  starting at 25  $\mu\text{g}$ /day and increasing every other week to 75  $\mu\text{g}$ /day. After 8 wk the subjects were crossed onto the other regimen. The effect of the  $T_3$  was only evident in the second 8 wk in the group crossed to  $T_3$ . In one 24-wk double-blind, placebo-controlled randomized study, 16 patients were given a diet of 800 kcal/day and spent most of the study time on a metabolic ward. The weight of the  $T_3$ -treated patients at the beginning of the study was  $134.9 \pm 6.2$  kg and the weight of the placebo-treated group was  $132.1 \pm 4.7$  kg. At week 8, when most patients had stayed in the metabolic ward, the weight loss of the  $T_3$ -treated group was  $13.1 \pm 1.0$  kg compared with  $7.9 \pm 1.7$  kg ( $P < 0.025$ ). After 24 wk in the trial, those treated with  $T_3$ , 75  $\mu\text{g}$  three times daily, had lost  $21.9 \pm 4.9$  kg compared with the smaller, but not statistically different, loss of  $13.4 \pm 6.0$  kg. During the last 12 wk of the trial, several patients spent only part of the time in the hospital and were less successful. The authors noted that in spite of the dose of 225  $\mu\text{g}$ /day, "The patients on L-triiodothyronine were surprisingly free of volunteered symptoms and all tolerated the dose . . . extremely well" (927). In another randomized, placebo-controlled cross-over trial lasting 10 wk, 16 patients were started on a 1,000 kcal/day diet as outpatients. They were assessed for their symptoms of hyperthyroidism before the study using an objective questionnaire by a physician not participating in the treatment protocol. After a 2-wk run-in period, five patients were allocated to begin  $T_3$  75  $\mu\text{g}$ /day three times a day for 4 wk, and the other seven were assigned to the placebo for 4 wk. At week 6 the patients were crossed over for the remaining 4 wk with 12 patients remaining in the trial to the end. During treatment with  $T_3$ , the serum concentration more than doubled. Only four of the treated patients could be assigned correctly based on the symptoms questionnaire (a by-chance assignment) consistent with the finding of few objective symptoms noted above. The weight change during placebo treatment was +3.2 kg and during the  $T_3$  period was -3.9 kg. Pulse increased on average from 79 bpm to 86 bpm.

### B. Adrenergic thermogenic drugs

1. *Ephedrine with and without caffeine.* Ephedrine is a PPA. The hydroxyl group on the  $\alpha$ -carbon prolongs its duration of action, and the methyl group on the  $\beta$ -carbon as well as the amino group increases its peripheral actions and decreases its central actions on adrenergic receptors. Ephedrine releases endogenous catecholamines and has been used for

more than 70 yr to treat asthma. It was combined with theophylline as a first line treatment for asthma in the 1970s.

Caffeine, a component of coffee and other plant extracts, is a xanthine along with theophylline and theobromine. Caffeine has been a part of foods for centuries. Caffeine and other xanthines prevent the body from becoming resistant to the effects of ephedrine by inhibiting the adenosine receptor and phosphodiesterase (940). Caffeine combined with ephedrine stimulates both  $\alpha$ - and  $\beta$ -adrenergic receptors. The  $\alpha$ -,  $\beta_1$ -, and some of the  $\beta_2$ -receptors down-regulate with time, while the  $\beta_3$ - and some of the  $\beta_2$ -receptors do not (940). This allows ephedrine with caffeine to become a selective  $\beta_2/\beta_3$ -agonist over time as the tremor, tachycardia, and nervousness lessen or disappear.

Blockade of  $\beta_1$ - and  $\beta_2$ -receptors using nadolol blunted the acute increase in oxygen consumption seen with caffeine and ephedrine, suggesting that 40% of the increase in oxygen consumption can be attributed to the  $\beta_3$ -receptor (941). Lonnqvist *et al.* (942), looking at visceral fat cells, demonstrated that the  $\beta_3$ -receptor sensitivity was enhanced 50 times in obesity. Women with upper body obesity have a resistance to lipolysis in their subcutaneous abdominal fat cells that is due to a decrease in  $\beta_2$ -receptor sensitivity but not the  $\beta_1$ -receptor. The sensitivity to noradrenaline stimulation of lipolysis in subcutaneous abdominal fat cells from women with upper body obesity was increased 5-fold after weight loss that was due to increased sensitivity of the  $\beta_2$ - but not  $\beta_1$ -receptor sensitivity. This resistance of the  $\beta_2$ -receptor is located at a posttranscriptional level of the protein kinase-hormone sensitive lipase level (943).

The mechanism by which ephedrine affects weight is, at least in part, due to its effect upon thermogenesis. Astrup *et al.* (944) demonstrated that the excess oxygen consumption compared with placebo in the 3 h after an oral dose of ephedrine of 1 mg/kg was  $1.3 \pm 1.1$  and  $1.2 \pm 1.1$  liters before and 2 months after chronic treatment with ephedrine 60 mg/day compared with an increase in oxygen consumption of  $7.0 \pm 2.3$  and  $6.9 \pm 1.8$  liters after 4 and 12 wk of continuous treatment ( $P < 0.01$ ). Obese subjects have been shown to have a reduced thermogenic response to cold exposure and to ephedrine. The thermogenic response to cold exposure was not affected by 5 wk of exercise training, but the thermogenic response to ephedrine was slightly improved ( $1.1 \pm 0.23$  vs.  $1.4 \pm 0.17$  kJ/kg lean body mass/180 min.  $P < 0.06$ ) (945). Thermogenesis may be only one way that ephedrine exerts its effect. Jonderko and Kucio (946) have demonstrated that ephedrine 50 mg orally significantly delays gastric emptying compared with a placebo. The amount of food remaining in the stomach after 90 min was  $70.3 \pm 5.1\%$  after placebo and  $80.9 \pm 3\%$  in the ephedrine group ( $P < 0.02$ ), which may represent a mechanism for decreased hunger.

*a. Short-term clinical trials.* Several clinical trials with caffeine, ephedrine, and ephedrine and caffeine have been reported (115, 944–957). Daly *et al.* (947) performed a double-blind, randomized placebo-controlled trial of aspirin 330 mg/day, ephedrine 75–150 mg/day, and caffeine 150 mg/day in 24 obese volunteers. More weight was lost in the treated group ( $2.2 \pm .07$  kg vs.  $0.7 \pm 0.06$  kg,  $P < 0.05$ ) and ( $-5.2$  kg vs.  $-0.03$  kg,  $P < 0.03$ ) at 8 and 20 wk, respectively.

Buemann *et al.* (948) in an 8-wk controlled trial of caffeine 600 mg/day and ephedrine 60 mg/day in 32 women demonstrated that the HDL cholesterol dropped only in the placebo group during weight loss ( $P < 0.05$ ). Breum *et al.* (949) conducted a double-blind trial in 103 obese women comparing weight loss using dexfenfluramine 30 mg/day with the weight loss of the combination of caffeine 600 mg/day and ephedrine 60 mg/day. At 15 wk there was significantly greater weight loss in the caffeine and ephedrine group, but only in those with an initial BMI greater than  $30 \text{ kg/m}^2$  ( $7 \pm 4.2$  kg vs.  $9 \pm 5.3$  kg,  $P < 0.05$ ) suggesting greater efficacy in larger subjects.

Pasquali *et al.* (950) treated obese subjects with ephedrine 75 mg/day, 150 mg/day, or placebo in a 3-month trial. At the end of the first and second month, the decrease in BMI was significantly greater in the ephedrine-treated groups ( $P < 0.01$ ), but this difference was lost by the end of the third month. In another study Pasquali *et al.* (951) compared ephedrine 150 mg/day and placebo in a double-blind randomized cross-over trial in women who had difficulty losing weight and had adapted to a low-energy intake. The ephedrine group lost  $2.24 \pm 0.61$  kg in 2 months compared with  $0.64 \pm 0.5$  kg in the placebo group using a 1-month washout ( $P < 0.05$ ).

In a third study, Pasquali *et al.* (952) investigated the effect of ephedrine 150 mg/day compared with placebo on body composition during a 6-wk very-low-calorie diet. This study used a balanced double-blind cross-over design in which the subjects received ephedrine for 2 wk. Although there was no difference in weight loss, ephedrine significantly reduced urinary nitrogen excretion ( $F = 8.22$ ,  $P < 0.008$ ), blunted the diet-induced fall in RMR ( $F = 6.54$ ,  $P < 0.021$ ), and increased the  $T_3$  to  $T_4$  ratio ( $F = 5.79$ ,  $P < 0.029$ ) (952).

Astrup *et al.* (953) evaluated various combinations of caffeine with ephedrine and found that 200 mg of caffeine with 20 mg of ephedrine, when given three times a day, are synergistic in their effects. Dulloo *et al.* (954) concluded that the adenosine receptor played a minor role in the mechanism of action of caffeine and ephedrine and that the effect could be mainly attributed to an inhibition of phosphodiesterase. Horton and Geissler (955) demonstrated that the addition of aspirin, which inhibits an inhibitor of the  $\beta$ -receptor, does not add further to the thermogenesis of a meal when added to caffeine and ephedrine.

Astrup *et al.* (956, 957) estimated that 20% of the action of ephedrine with caffeine in promoting weight loss is due to increased metabolic rate while 80% is due to appetite suppression. He reached this conclusion in a study of 14 obese women who participated in an 8-wk double-blind placebo-controlled trial using a 1000 kcal/day (4.2 mJ/day) diet and caffeine 200 mg with ephedrine 20 mg three times per day. Weight loss was not different between the two groups ( $10.1 \pm 0.4$  vs.  $8.4 \pm 1.2$  kg), but the caffeine and ephedrine group lost 4.5 kg more body fat than the placebo group and less FFM ( $-1.1 \pm 1.4$  vs.  $-3.9 \pm 1.7$  kg) as measured by bioelectrical impedance analysis ( $P < 0.05$ ). The decrease in energy expenditure was blunted in the caffeine and ephedrine group at 8 wk ( $-15.6 \pm 2.4$  vs.  $-26.5 \pm 3.7$  kJ/kg FFM/day), and all of the increased energy expenditure in this group was accounted for by an increase in fat oxidation ( $P < 0.001$ ).

corresponding to a decrease of 8% vs. 13% (957). Fat loss and lean gain provide the energy lost over the 56 days of this trial. Only 20% of this loss is reflected in the blunting of the decline in energy expenditure. Thus, the other 80% must reflect a decline in energy intake.

*b. Long-term clinical trials.* In a 6-month trial, Astrup *et al.* (115) compared placebo, caffeine 600 mg/day, ephedrine 60 mg/day, and the combination of caffeine 600 mg/day with ephedrine 60 mg/day in 180 obese subjects (Fig. 18). Withdrawals were equal in all groups and 141 subjects completed the trial. Weight loss was significantly greater in the group receiving both caffeine and ephedrine ( $16.6 \pm 8.6$  kg vs.  $13.2 \pm 6.6$  kg,  $P < 0.0015$ ). Weight loss in the caffeine-only group and the ephedrine-only group was not different from that in the placebo group. Side effects of tremor, insomnia, and dizziness were transient and by 8 wk were no different than the placebo group. Blood pressure fell equally in all four groups. After 6 months the medication was stopped for 2 wk to assess withdrawal symptoms. One hundred twenty-seven subjects then entered a 6-month open-label study of caffeine 600 mg/day with ephedrine 60 mg/day (115). The 99 subjects who completed the study lost an additional 1.1 kg ( $P < 0.02$ ), and no clinically significant withdrawal symptoms were observed (Fig. 18). Caffeine and ephedrine, like phentermine and fenfluramine in the one other long-term controlled trial that combined two medications for weight loss, gave 16% loss of initial weight over 6 months that was maintained for the remainder of the year of treatment.

In a 15-wk comparison between dexfenfluramine (30 mg/day) compared with caffeine 200 mg and ephedrine 20 mg three times daily in obese subjects with a BMI greater than  $30 \text{ kg/m}^2$  (949), the group receiving caffeine with ephedrine lost more weight ( $7 \pm 4.2$  kg vs.  $9 \pm 5.3$  kg  $P < 0.05$ ).

*2. Terbutaline.* Terbutaline is a  $\beta_2$ -agonist used to treat asthma. Studies with terbutaline suggest that the effect of caffeine and ephedrine on body composition and oxygen consumption may be attributable to  $\beta_2$ -adrenergic stimulation. Scheidegger *et al.* (958, 959) demonstrated that terbutaline 15 mg/day for 2 wk significantly increased BMR ( $5.04 \pm 0.167$  vs.  $5.421 \pm 0.234$  kJ/min,  $P < 0.05$ ), insulin-stimulated glucose disposal

by improving nonoxidative glucose storage ( $7 \pm 0.47$  vs.  $9.05 \pm 0.67$  mg/min/kg,  $P < 0.02$ ), and the ratio of  $T_3$  to  $T_4$  ( $19.4 \pm 1$  vs.  $24.4 \pm 1$ ,  $P < 0.001$ ). Acheson *et al.* (960) studied healthy young men in a 6-wk cross-over trial. The subjects took propranolol 160 mg/day or terbutaline 15 mg/day for 2 wk followed by a 2-wk placebo period and were then switched over to the drug they had not taken in the first 2-wk period. The last 2 days of each period were spent in a metabolic chamber where energy expenditure and metabolic balance were measured. Significant differences were observed between propranolol, placebo, and terbutaline, respectively, for heart rate ( $65 \pm 3$ ,  $75 \pm 4$ , and  $84 \pm 4$  bpm), nitrogen excretion ( $13.6 \pm 0.7$ ,  $12.6 \pm 0.6$  and  $11.9 \pm 0.6$  g/day), fat oxidation ( $1,045 \pm 95$ ,  $1,243 \pm 148$ , and  $1,278 \pm 84$  kcal/day), and the  $T_3$  to  $T_4$  ratio ( $12 \pm 0.7$ ,  $15.7 \pm 0.9$ , and  $17.2 \pm 1$ ). This suggests that stimulation of  $\beta_2$ -receptors increases metabolic rate through an increase in fat oxidation and a conservation of lean body mass, similar to the re-partitioning effect of ephedrine and caffeine noted above (957).

*3.  $\beta_3$ -Adrenergic agonists.* It has been known for a long time that NE will stimulate thermogenesis in experimental animals, and that this stimulatory response is enhanced with cold exposure (961). One site of action for this response is brown adipose tissue (962). This tissue is abundant in newborn animals and is believed to be important in maintaining thermoregulation in the newborn (959). Blockade with  $\beta$ -adrenergic drugs in newborn mammals will cause marked hypothermia (959). In the newborn and after cold exposure, the brown adipose tissue cells increase the density of their mitochondria, which is believed to be the source of the heat production in this tissue by opening of a proton leak in the mitochondrial membrane.

An additional function for brown adipose tissue was suggested by the finding that this tissue hypertrophied when young animals were given a diet of highly palatable food. Stock and Rothwell (962) showed that brown adipose tissue played a role in the response to these diets by dissipating additional calories rather than storing them. In the animal that has overeaten a highly palatable diet, the thermogenic response to NE is accentuated, and is blocked by propran-

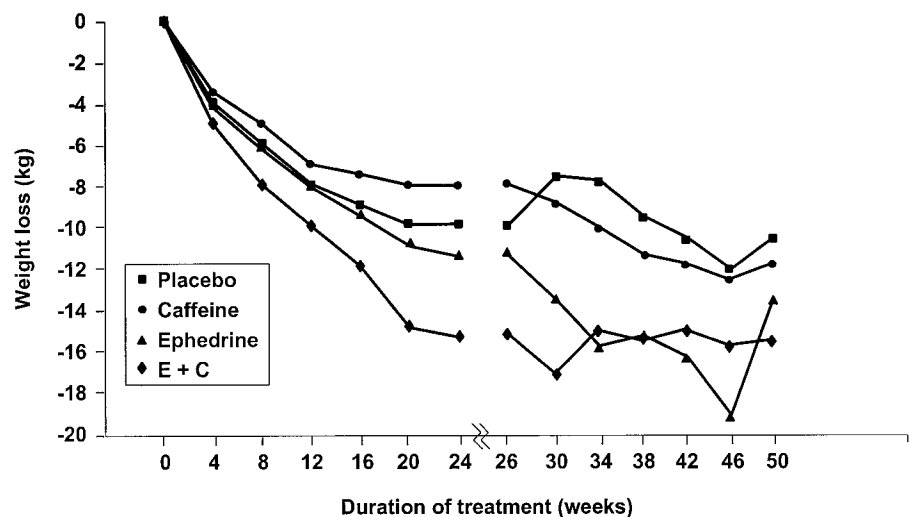


FIG. 18. Effect of ephedrine and caffeine on weight loss and weight maintenance for 1 yr. [Adapted with permission from A. Astrup *et al.*: *Int J Obes Relat Metab Disord* 16:269–277, 1992 (115).]

olol, indicating that  $\beta$ -adrenergic receptors are involved (962).

Studies of the mitochondria from brown adipose tissue revealed that it has a functional proton leak that could be activated by NE. Guanosine-5'-diphosphate is an inhibitor of this channel (961). The quantity of uncoupling protein or UCP-1 is increased in animals exposed to the cold and in animals eating a highly palatable or cafeteria diet (960, 961). Ricquier and colleagues (966, 967) cloned the gene for this proton channel that is located on the inner mitochondrial membrane. The sequence and regulatory regions of the gene that produces UCP-1 are known, and it has elements that increase transcription in the presence of NE (968).

Using probes from the cDNA sequence of UCP, two other uncoupling proteins have recently been identified. They are called UCP-2 and UCP-3 to distinguish them from UCP-1, which is the one that predominates in brown adipose tissue. UCP-2 is widely distributed but is not thought to be controlled by NE. UCP-3 has only recently been identified, and its regulation is not known (969–971).

NE stimulates lipolysis in white adipose tissue by activating  $\beta$ -adrenergic receptors (972). Recognizing that there was probably an additional receptor besides two "classic"  $\beta_1$ - and  $\beta_2$ -receptors, Strosberg (973) cloned a new  $\beta$ -adrenergic receptor, the  $\beta_3$ -receptor that is found predominantly on brown but also white fat cells, as well as in the colon and gall bladder, and possibly the stomach. The  $\beta_3$ -adrenergic receptor, like the other  $\beta$ -receptors, has seven membrane-spanning sequences, a receptor site on the N-terminal chain, and a long third intracellular loop. In contrast with the other two  $\beta$ -adrenergic receptors, the  $\beta_3$ -adrenergic receptor is not "down-regulated" by treatment with  $\beta$ -agonists (973).

Because the  $\beta_3$ -adrenergic receptor mediated the thermogenic response to NE, it was an ideal candidate for pharmaceutical development of agonists (974, 975). The first generation of phenethanolamine agonists was developed against the rat receptor using lipolysis in white adipose tissue as an assay. A few of these compounds were tested in human beings, and the data are summarized in Table 21. Four drugs demonstrated an increase in energy expenditure, which was usually associated with increased heart rate (BRL 26830A; BRL35135; Ro16–8714; Ro40–2148). Clinical trials in obese patients have been with BRL 26830A, BRL35135, and Ro40–2148 (Table 21). The limited responses in humans may reflect the fact that the first generation of agonists was developed against rat receptors.

The only first generation atypical  $\beta$ -adrenergic agonist to have a long-term clinical trial is BRL 26830A (R\*,R\*)-( $\pm$ )-methyl-4-[2-[(2-hydroxy-2-phenylethyl)amino]propyl]-benzoate,(E)-2-butenedioate (2:1) (976–984). This drug stimulates oxygen consumption in the genetically obese leptin-deficient *ob/ob* mouse and causes weight loss and a decrease in body fat, but conserves or increases lean body mass (974). The drug also stimulates lactate production and inhibits glycogen synthesis in skeletal muscle from rats. It stimulates oxygen consumption in human beings for up to 6 wk (988).

Connacher *et al.* (116) conducted an 18-wk double-blind randomized trial in 40 obese patients. They were prescribed an 800-kcal, low-fat, high-fiber diet. The subjects received 200 mg daily for 2 wk and then 400 mg daily or placebo for 18

wk. There were 4 dropouts in each group. The experimental group lost  $15.4 \pm 6.6$  (SD) kg in 18 wk, compared with  $10.0 \pm 5.9$  (SD) kg in the placebo group ( $P = 0.02$ ). The metabolic rate decreased less in the experimental group (5.35 to 5.11 kJ/min) than in the placebo-treated group (5.22 to 4.98 kJ/min) ( $P = 0.08$ ). An increase in tremor, probably related to activation of  $\beta_2$ -adrenergic receptors, was the principal drawback (982, 983). In a behavioral evaluation the drug had no adverse influence on hunger or satiety (985).

BRL-35135 is structurally similar to BRL 26830A with a substitution of a Cl on one phenyl ring and a different carboxy structure on the other phenyl ring. Mild tremor noted with BRL 26830A was also seen with this drug (986, 987). The drug increases RMR and along with BRL-26830A (984) improves glucose tolerance (986, 988). The ICI-D7114 compound developed using the rodent receptor assays was nearly devoid of thermogenic properties (990). A pair of compounds developed by Hoffmann LaRoche (Nutley, NJ) (Ro 16–8714 and Ro 40–2148) were thermogenic in lean and obese subjects (991–994) but also produced significant increases in heart rate. The final compound from the rodent receptor assays (CL-316, -243, or BTA-243) was not thermogenic but in a short-term clinical trial improved glucose disposal (995).

With the cloning of the  $\beta_3$ -receptor from human beings (973, 996), which is different than the rat receptor, the door was opened to developing  $\beta_3$ -agonists that were selective for this receptor. Several compounds appear to have reached early evaluation, but no clinical trials are known to be underway.

## VI. Conclusion

Several things became apparent during the course of preparing and writing this review. First, the quality of clinical trials that have evaluated antiobesity drugs in the last quarter of the century are much improved over those conducted during the third quarter of the century. In this earlier period the trials were generally of short duration, were often cross-over in design, had small numbers of subjects that underpowered them, and the reports were often lacking in detail. Between the approval of chlorphentermine, clortermine, mazindol, and fenfluramine in 1973 and the approval of dexfenfluramine in 1996, the clinical trials had increased in length, were more often multicenter, used many more subjects to provide the needed power, and sometimes used stratification to balance the groups. All of these procedures have greatly improved the data available for review. At hearings before the FDA in 1995, one of us (G.A.B.) had expressed doubts about the possibility of conducting two-year trials because the placebo group would have a tendency to drop out because of inadequate weight loss. This has been disproven by the 2-yr double-blind randomized placebo-controlled trial of orlistat that was recently published.

The basis for short-term trials earlier in this century was the belief that if patients lost weight they would be able to keep it off. That is, there was an underlying assumption that obesity could be cured. This has proven wrong, and obesity is now viewed as another chronic disease that requires long-



TABLE 21. Clinical studies with  $\beta_3$ -agonist

Author	Year	Subjects	Duration	Diet	Energy expenditure	Heart rate		Weight loss		Comments
						Placebo	Drug	Placebo	Drug	
BRL 26830A										
Zed <i>et al.</i> (977)	1985	Obese 16 (14 F; 2 M)	6 wk	Restricted				-6.56 kg -7.3%	-9.34 kg -10.1%	RCT wt 92.7 kg (D) 89.8 kg (P)
Abraham <i>et al.</i> (978)	1987	Obese	6 wk	Restricted				-232 g/day	-201 g/day	RCT-Metabolic balance
Smith <i>et al.</i> (980)	1987	Lean (12 M)	10 days	None						RCT Fasting insulin ↓
Chapman <i>et al.</i> (981)	1988	Obese (43 postmeno- pausal F)	6 wk	1000 kcal/ day		No change		+0.3 kg	-0.2 kg	RCT 50 mg g/day Tremor
Connacher <i>et al.</i> (116)	1988	Obese 20 20	18 wk	800 kcal/ day	REE ↑ 11.6%	No change		10.0 ± 5.9 kg		RCT 200 mg/day × 2 wk then 400 mg/day
Connacher <i>et al.</i> (982)	1990	18		Single dose						Tremor increased
Connacher <i>et al.</i> (984)	1992	Obese (12 F)	3 wk	No diet	No acute drug effect on VO <sub>2</sub> or RQ	No change		None		Metabolic study 100 mg tid improves insulin sensitiv- ity. Down-regulates adren- ergic receptors selectively
BRL 35135										
Mitchell (986)	1989	Obese (6 F; 4 M)	10 days	Wt main- taining diet	No change in glucose- induced thermogen- esis	No change		No change		Metabolic study Mild tremor; improved glu- cose tolerance
Smith <i>et al.</i> (987)	1990	NIDDM								Mild Tremor
Cawthorne <i>et al.</i> (988)	1992	Lean M	Single dose		↑ Glucose-induced thermogenesis (GIT)					Improved glucose tolerance
ICI D7114										
Toubro <i>et al.</i> (989)	1993	Lean	14 days		No change					No effect on glucose disposal
Goldberg <i>et al.</i> (990)	1995	Lean M (16)	14 days		No change in sleeping EE			No change		Parallel arm-RCT
Ro-16-8714 (Ro 40-2148)										
Henny <i>et al.</i> (991)	1987	Lean M	14 days		Increased	↑				
Henny <i>et al.</i> (992)	1988	Lean (6) Obese (6)	14-day single dose		Increased REE (12.2%)	↑				BP ↑
Jecquier <i>et al.</i> (993)	1992				Increased REE (14.4%)	↑				
					REE ↑ 10% with 5 mg 21% with 20 mg	↑ 8% ↑ 49%				Review; 5 and 20 mg
CL 316,243 (BIA-243)										
Haesler (994)	1994	Obese F	14 days		Resting EE un- changed Glucose-induced EE ↑	No change				Single-blind 400 mg bid RQ unchanged
Wheeldon (979)	1994	Lean M (8 M)	Single dose with blockers	No diet	REE ↑ partly blocked by nadol Salbutamol ↑ REE blocked by $\beta_2$ Antagonist					K <sup>+</sup> ↓ vs salbutamol
Weyer (995)	1998	Lean (14 M)	8 wks	No diet	No change	No change		None		Parallel arm lowered RQ FFA ↑ non-oxidative glu- cose disposal

F, Female; M, male; REE, resting energy expenditure; RQ, respiration quotient; tid, three times daily; bid, twice daily; RCT, randomized clinical trial.

term treatment when the risk is sufficiently high. This changing attitude is reflected in the need for longer-term efficacy and safety data. Adding to this need for long-term data was the regain in weight of many patients treated with fluoxetine and sertraline after their initial weight loss. These drugs became ineffective in chronic treatment, indicating the need to document chronic effectiveness for any drug that would be used.

The third important message we obtained from reviewing this literature was the rapid expansion in biological understanding of obesity (993). After World War II it was the anatomic studies of hypothalamic obesity that were center stage. This was followed by recognition of the monoamines as neurotransmitters in the regulation of food intake and of fat cells as the repository for the excess fat. The last quarter century has seen an explosion of additional information including the role of the GI tract and vagus in afferent signals; the role of peptides in modulating central control of feeding; the efferent controls in the sympathetic and parasympathetic nervous system and the permissive role of adrenal glucocorticoids; and finally of the important and central role of the fat cell in providing the leptin signal for long-term regulation of body fat stores. Against this rapidly expanding base of knowledge, the potential for new and innovative strategies for treatment of obesity is around the corner (997).

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**14th International Symposium of  
The Journal of Steroid Biochemistry  
& Molecular Biology**

*RECENT ADVANCES IN STEROID BIOCHEMISTRY & MOLECULAR BIOLOGY*

**June 24–27, 2000–Quebec, Canada**

The 14th International Symposium of The Journal of Steroid Biochemistry & Molecular Biology—*Recent Advances in Steroid Biochemistry & Molecular Biology*—will be held in Quebec, Canada, on June 24–27, 2000. The following topics will be considered:

1. Steroid Receptors, Structure, and Mechanism of Action
2. Anti-Steroids
3. Steroids and Cancer
4. Control of Steroidogenesis, Including Defects in Steroid Metabolism
5. Enzyme Inhibitors
6. Steroids and the Immune System
7. Steroids and the Menopause

Lectures (approximately 25–30) will be by invitation of the Scientific Organizing Committee and, in addition, there will be a poster section. All poster presentations will be subject to selection by the Scientific Organizing Committee and abstracts (maximum 200 words) must be sent to Dr J. R. Pasqualini by Monday, February 14, 2000 (postmark) (ORIGINAL + 12 copies). For further details, please contact:

General Scientific Secretariat:

Dr J. R. Pasqualini  
Steroid Hormone Research Unit  
26 Boulevard Brune  
75014 Paris  
France

Tel.: (33-1)+45 39 91 09/45 42 41 21  
Fax: (33-1)+45 42 61 21  
e-mail: Jorge.Pasqualini@wanadoo.fr

Local Organizing Committee:

Dr F. Labrie  
MRC Group in Molecular Endocrinology  
CHUL Laval, Centre de Recherches  
2705 Boulevard Laurier  
Ste-Foy, Quebec G1V 4G2, Canada

Tel.: (418)+654 27 04  
Fax: (418)+654 27 35  
e-mail: Fernand.Labrie@crchul.ulaval.ca