Drug treatment of obesity\textsuperscript{1,2}

George A Bray

\textbf{ABSTRACT} The currently available drugs for treatment of obesity act on two pharmacologic systems in the central nervous system: the noradrenergic system and the serotonergic system. There are clear and convincing clinical data that these drugs are effective and safe. However, several types of barriers exist to their proper and effective use, including public perceptions that obesity is a disease resulting from lack of willpower, professional expectations that anorexiant drugs should cure obesity, hindrance by state licensing agencies, regulatory rigidity, limited research funding, and legislative inaction. In spite of these limitations, several new and potentially valuable drugs are under development, and given an appropriate clinical and therapeutic environment, the future is bright for treatment of obesity. \textit{Am J Clin Nutr} 1992;55:538S–44S.

\textbf{KEY WORDS} Anorexiant drugs, noradrenergic drugs, serotonergic drugs, stigmatization, thermogenic drugs

\section*{Introduction}

Drugs for the treatment of obesity can be classified by using a feedback model to understand alterations in nutrient balance (1). A feedback model consists of a control system of nutrient intake, digestion, absorption, storage, and oxidation, which sends afferent messages of a hormonal, neural, or nutrient type to a central controller in the brain, which in turn sends efferent signals to regulate digestion and metabolism of food and the partitioning of nutrients between fat, protein, and energy utilization. A classification of treatments for obesity by use of this approach is shown in Table 1 (2).

\section*{Drugs acting on the central nervous system}

\textit{Drugs acting on noradrenergic neurotransmitters}

Most appetite-suppressing drugs currently marketed for the treatment of obesity are derivatives of phenethylamine (3, 4). The exception is mazindol, which is an imidazaoisoindole. The currently available drugs are listed in Table 2 according to the Drug Enforcement Agency (DEA) Schedule.

Pharmacologic effects. The pharmacologic effects of appetite suppressants can be divided into three categories. 1) Most of these medications can stimulate the central nervous system, but the degree is highly variable; and two of them, phenylpropanolamine and fenfluramine, appear almost devoid of this effect. 2) Some appetite-suppressing drugs have cardiovascular effects, which include a rise in heart rate and blood pressure, but most do not. A rise in heart rate and blood pressure has been observed with amphetamine, methamphetamine, ephedrine, and phenmetrazine but is minimal or absent with the others. Moreover, weight loss may actually lower blood pressure. 3) Metabolic effects expressed as a rise in the concentration of free fatty acids and/or glycerol in plasma have been observed after administration of amphetamine, methamphetamine, and fenmetrazine. Methamphetamine has been found to antagonize the lipolytic effects of norepinephrine in vitro but has no direct lipolytic effect itself. Mazindol has been reported to increase the uptake of glucose after intravenous administration in humans. Fenfluramine reduces blood glucose through non-insulin-dependent mechanisms (4).

The peak blood concentration of anorexiant medications usually occurs shortly after oral administration. However, the half-life of the drugs in the serum varies considerably; benzphetamine and amphetamine have 2–5-h half-lives compared with much longer ones for phentermine, fenfluramine, and fluoxetine (a serotonergic antidepressant that has been reported to produce weight loss but has not been approved for that indication, see below). There are important pharmacologic differences among the stereoisomers of these compounds. The dextro isomer of amphetamine, for example, is four times more potent than the levo isomer. The d-isomer of fenfluramine appears to contain most, if not all, of the appetite-suppressing effects of the racemic (d, l) mixture with the l-isomer being ineffective in this regard. Urinary excretion of several drugs is dependent upon urine pH and may increase in acidic urine (4).

\textit{Clinical use of noradrenergic appetite-suppressing drugs}. In evaluating the clinical usefulness of appetite suppressants, two questions need to be answered: Are they effective? And are they safe?

The Food and Drug Administration has provided one of the largest reviews of effectiveness for noradrenergic drugs (5). They analyzed 105 new drug applications containing data on 4543 placebo-treated and 3182 patients treated with active drugs. In studies comparing placebo and active drug, the dropout rate after 4 wk of therapy was 18.5\% for subjects on placebo and 24.3\% for those receiving active drug. At the end of the study periods, lasting 3, 4, 8, or more weeks, equal percentages of patients receiving placebo and active drugs remained in treatment (49\% for the placebo group vs 47.9\% for the active-drugs

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TABLE 1
A nutrient balance approach to treatment of obesity

<table>
<thead>
<tr>
<th>Component</th>
<th>Mechanism</th>
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<tr>
<td>Agents acting on controlled system</td>
<td>Decrease nutrient density of food</td>
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<td>Reduce digestibility</td>
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<td>Exercise</td>
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<td>Change nutrient partitioning</td>
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<td>Agents acting on afferent system</td>
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<td>Taste altering drugs</td>
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<td>3,4-Dihydroxybutyrate</td>
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<td>Nutrients</td>
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<td>Adrenergic agonists (α-1, β-3)</td>
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<td>Peptides</td>
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<td>β-3 Agonists</td>
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<td>Agents acting on efferent mechanisms</td>
<td>Thermogenic drugs</td>
<td>Adrenalectomy</td>
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<td>Jaw-wiring</td>
<td>RU-486 blockade of steroid receptors</td>
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<td>Steroid removal</td>
<td>Dopamine agonists</td>
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Drug-treated patients lost on average 0.25 kg/wk (0.56 lb/wk) more than subjects receiving placebos.

The effectiveness of weight loss by anorexiant medications can also be evaluated in terms of the proportion of subjects who lost given amounts of weight per week. A weight loss of ≥ 0.45 kg/wk was almost twice as common in patients receiving active drugs (44%) as in those on placebo (26%), as was a weight loss of ≥ 1.4 kg/wk, achieved by 2% of those on active drugs compared with 1% of those on placebo. An examination of the weight loss results after 4 wk of treatment shows 68% of patients on the active drugs lost ≥ 0.45 kg/wk compared with 46% patients on placebo and 10% of the drug-treated subjects vs 4% of those receiving placebo lost ≥ 1.4 kg/wk. In clinically effective doses there was no basis on which to choose between these drugs in...
terms of their rates of weight loss or the duration over which 
this weight loss occurred (5). The data from one 20-wk trial are 
shown in Figure 1.

Additional data are available from trials lasting from 6 to 52 
wk (4). Weight loss continued at a decelerating rate for the du-
ration of treatment. Tolerance did not appear to develop, since 
increased amounts of drug were not required to maintain weight 
loss.

Phenylpropanolamine is the only noradrenergic drug that is 
available for weight control over-the-counter (Table 2). It is also 
sold in many nasal decongestants. In a review of this drug, an 
advocacy team to the Food and Drug Administration concluded 
that it was probably safe and effective. At high doses (75 mg) it 
has been reported to increase blood pressure. A critical review 
of published and unpublished studies with this drug supports 
this contention (6). In one group of five clinical trials with phen-
ylpropanolamine alone, the drug-treated individuals lost an av-
erage of 0.24 kg/wk more than the placebo-treated group. This 
is very similar to the extra weight loss of 0.25 kg/wk reported 
when prescription appetite-suppressing drugs and placebo 
are compared. A more recent study (6) illustrated the effectiveness 
of phenylpropanolamine with minor adverse effects, particularly 
over the critical holiday period.

Drugs acting on serotonin neurotransmitters

Pharmacology: One of the general biobehavioral properties 
of serotonin is a reduction in the physiological level of activity, 
including food intake. Drugs modulating serotonin metabolism 
fluence body weight (4). Food intake is reduced by the ad-
ministration of tryptophan or 5-hydroxytryptophan, two pre-
cursors that are converted to serotonin after entering the brain. 
Similarly, drugs that release serotonin from nerve endings (fen-
fluramine) and/or block its reuptake (fluoxetine or sertraline) 
decrease food intake and body weight. Fenfluramine was the 
first clinically useful appetite-suppressant medication of this type 
(Table 2). It both releases and prevents reuptake of serotonin.

Clinical trials with serotonergic drugs. Trials with serotonergic 
drugs have lasted up to 52 wk. In one trial (8, 9), fenfluramine 
was administered continuously for 1 y, followed by a second 
year of placebo (Fig 2). A plateau of weight loss occurred between 
the 8th and 12th month and weight remained 10-11 kg lower 
for the remainder of the year. When transferred to placebo, pa-
tients regained weight as would be expected when treatment for 
a chronic disease is stopped.

A second year-long trial with d-fenfluramine vs placebo shows 
that a nadir occurred after a weight loss of 11% of initial weight 
(10). Those in the placebo group plateaued after a weight loss 
of 8% (Fig 3).

A third study has compared the combined effect of a seroto-
nergic drug, d-fenfluramine, plus a noradrenergic drug, phen-
termine. After a single blind run-in period of 4 wk, the drug-
treated patients reached a nadir that was 17 kg below the placebo
WEEKS OF TREATMENT

2 MONTHS

DRUG TREATMENT OF OBESITY

FIG 1. 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 finished the 20-wk trial. (To convert pounds to kilograms divide by 2.2.) (Copyright 1976, George A Bray).

weight level and that was maintained until the end of the 34-wk trial (M Weintraub, personal communication, 1991).

Three clinical findings from these studies would argue against tolerance. 1) Weight loss continued for 4–6 mo until a new plateau was reached. 2) Hunger did not increase during treatment. 3) Subjects regained weight when fenfluramine was discontinued. One interpretation of this is that the drug had readjusted the weight-control mechanism to a lower level, which ceased when the drug was stopped (11).

Safety of appetite suppressants

The safety of appetite suppressant drugs has been the subject of considerable discussion (4). Griffiths et al (12), using baboons as subjects, examined the reinforcing properties of intravenous preparations of several appetite-suppressing drugs and compared them to the reduction in food intake. The reinforcing property is the effect of a drug that leads the animal to seek additional amounts of the drug. The ratio of anorexiant dose to reinforcing dose, a measure of abuse potential, is shown for several drugs in Figure 4. At one extreme is diethylpropion and amphetamine, which show a small reinforcing effect; at the other extreme is fenfluramine and phenylpropanolamine, which have no reinforcing effect. Although the ratio of appetite-suppressant dose to reinforcing dose may help predict abuse potential, it does not always correlate with clinical experience. For example, diethylpropion has been widely used as an appetite-suppressing drug, with few reported episodes of abuse. However, its ratio of appetite-suppressant to reinforcing is greater than that of amphetamine or phenmetrazine, which have both been abused with addictive results and are appropriately classified in Schedule II. There is no indication for use of drugs in Schedule II for the treatment of obesity (3, 4). Drugs in Schedule IV are obviously preferred, but drugs in Schedule III also have a low abuse potential.

Barriers to use of current drugs

Clinical and experimental data suggest that anorexiant drugs have little risk (3, 4). Drug abuse with amphetamine, methamphetamine, and phenmetrazine is well-known and these drugs have no place in the treatment of obesity and are not approved for this purpose. However, the other drugs have little abuse potential and in studies that use drug reinforcement protocols two drugs, phenylpropanolamine and fenfluramine, have been shown to have no reinforcing properties, indicating essentially complete freedom of abuse potential. Likewise, side effects other than dry mouth, alterations in bowel habits, and insomnia are relatively mild.

FIG 2. Mean weight change during 1 y of treatment with dl-fenfluramine. A total of 176 patients were followed for 1 y of drug treatment and for a second year after discontinuation of the drug. (To convert pounds to kilograms divide by 2.2.) (Adapted from reference 8 and published in reference 9).
This profile of relatively safe drugs with long-term effectiveness leads one to ask why they are not more widely used (3). There are a number of barriers to the effective use of anorexiant agents. First, obesity is a stigmatized condition. That is, the public perceives obesity not as a disease, as proposed by the 1985 NIH Consensus Conference (13), but rather a condition associated with a lack of willpower and gluttony. Willpower, the power to push oneself away from the table, is all that is needed to treat obesity. This simplistic public perception of obesity is reflected in professional attitudes of health-care workers as well (14).

The fact that obesity patients regain weight after treatment is terminated is almost universally attributed to a failure of the drugs because health professionals expect that after drug treatment of obesity there should be no weight regain. That is, the drugs are expected to cure obesity. These professional attitudes have lead to a demand for higher therapeutic standards for medications used in treating obesity than for medications used in treating other chronic conditions. In a recent review, Weintraub and Bray (3) described this unrealistic expectation as follows: “We accept the fact that serum cholesterol values will rise following the cessation of therapy with hypocholesterolemic drugs. We also accept that peptic ulcers will also recur following cessation of H2-blocking medications. We understand rising intraocular pressure when pilocarpine treatment is stopped, meaning that glaucoma has been controlled but not cured. Even in the absence of a cure, patients and physicians still view ocular hypotensive agents, cholesterol lowering medications and H2-blockers as valuable. All of these failures to cure a problem of malregulation in the human organism are acceptable. Yet, for obesity, this is unacceptable” (3).

Barriers to the effective use of anorectic drugs are also provided by state licensing agencies. Many physicians have been questioned and disciplinary action brought for using appetite-suppressant drugs for “more than a few weeks”. Yet the available data reviewed above argue they are effective for as long as they are used. Regulatory rigidity in scheduling and labeling anorexiant drugs is also a barrier to their effective use. The Food and Drug Administration has labeled these drugs for “the management of exogenous obesity as a short term (a few weeks) adjunct” to the treatment of obesity. There is no definition of exogenous, a term of dubious and outmoded merit in describing obesity.

The data do not support a few weeks unless this means 34–52 wk or more. Clearly, regulations do not make truth, and current regulations appear to bear little relationship to the realities associated with these medications. Even worse, unrealistic regulations can serve as the basis for criminal prosecutions, without the perpetrators of the regulations being liable for the negligence that they have produced. Moreover, current regulations inhibit future developments because they indicate a closed and unresponsive legalistic mentality from regulatory authorities.

Another limitation in the use of anorexiant drugs has been the relatively limited number of clinical trials possible because of limited research funding. Few, if any, of the current medications have patent protection and thus there is no incentive for companies to conduct long-term trials. Government spending is limited: $35 million spent on obesity research against expenditures by the public of more than $35 billion in its quest for leanness. There is only a single Obesity Research Center where trials could effectively be done. Finally, the legislative process has produced hearing reports on the diet-pill industry in 1967, on the liquid-diet fiasco in 1977, and the obesity treatment programs in 1990, but it has produced little increase in funding.

Other drugs, and drugs under development

Centrally active drugs

Naloxone, a drug which blocks the action of opioids and decreases food intake in experimental animals, has also been demonstrated to decrease food intake acutely in normal-weight and overweight subjects (15), but the longer acting naltrexone has not been effective (16). A number of peptides can increase or decrease food intake in experimental animals (17). Of these,
neuropeptide-Y, galanin, corticotropin-releasing hormone, and cholecystokinin have received the most emphasis.

**Thermogenic drugs**

_Thyroid hormone_. Thyroid hormone is one prototype of a thermogenic drug. It produces a log-dose increase in metabolic expenditure. However, pharmacologic doses, and even high physiological doses, of thyroid hormone are associated with increased breakdown of protein, increased calcium loss from bone, and an increased risk of cardiovascular dysfunction. There is thus no current indication for use of thyroid hormone for treatment of obesity, except as replacement therapy for clinical and laboratory-documented hypothyroidism.

Ephedrine. Ephedrine is a synthetic adrenergic drug having both α- and β-agonist properties. Ephedrine may increase blood pressure, heart rate, and peripheral vascular resistance. Central nervous system stimulation may occur. Some people cannot tolerate the central nervous system effect, complaining of insomnia and nervousness. However, ephedrine can increase energy expenditure when administered orally. At present the data are insufficient to conclude that ephedrine alone is useful in treating obesity (11). A recent report by Astrup et al (18) showed that when ephedrine is combined with caffeine significant weight loss can be induced.

Beta-adrenergic agonists. The observation that β-adrenergic drugs could enhance thermogenesis in experimental animals has led to the development of other thermogenic compounds (19). Treatment of experimental animals with these drugs will decrease body weight and body fat content without reducing food intake, suggesting that they work by increasing energy expenditure. Two of three clinical trials with a β-agonist (BRL26830A) have resulted in desirable weight loss (20, 21). Results in the other were equivocal (20). The presence of tremor of the hands (a β2-adrenergic effect) and an increase in heart rate have led to the search for drugs with a better pharmacologic profile (22).

_Growth hormone_. Growth hormone is calorigenic (3) and has been shown to reduce protein loss during low-calorie dieting. However, growth hormone remains controversial and experimental. The adverse effects of growth hormone, including development of acromegaly, make its use problematic.

**Drugs affecting the gastrointestinal tract**

Because the taste of food, its digestibility, and its metabolism are related to the control of food intake, it is not surprising that approaches that alter these factors have been selected for development of medications for treatment of obesity. Several different drugs that modify the taste, digestion, or absorptive processes in the gastrointestinal tract have been tested.

_Enzyme inhibitors_. Inhibition of fat digestion or absorption reduces the available energy from fats in the diet. The antibiotic neomycin will increase the fecal excretion of fat, but the changes in the intestinal mucosa caused by this drug make it unacceptable for clinical use in obesity (3). Cholestyramine is a resin that binds bile salts and thus disturbs micelle formation. When given to obese patients in large doses this drug does not increase fat loss significantly and is thus ineffective in obesity (3). Drugs that inhibit disaccharidase enzymes in the intestine have also been tried but have not been shown to increase weight loss over diet alone. Finally, a lipase inhibitor, tetrahydrolipostatin, has recently been described. In animal studies it appears promising and clinical trials are underway (23).

_Indigestible food_. Sucrose polyester (Olestra, Procter and Gamble, Cincinnati) is an indigestible fat produced by esterifying sucrose with fatty acids of appropriate length to give it characteristics of a normal cooking oil. Addition of this agent to the diet will reduce the absorption of cholesterol and vitamin A by 67% and 42%, respectively. In one clinical trial with sucrose polyester, overweight subjects did lose weight (24). A subsequent study by Mellies et al (25) failed to demonstrate any significant effect on body weight of substituting sucrose polyester for fat in the diet of five obese subjects. The reasons for the reduction in caloric intake in one study and the failure to detect a reduction in the second study remain unclear. Recent data show that in normal-weight subjects, adaptation does occur (26).

_Inhibitors of gastric emptying_. Another area for potential therapeutic intervention is gastric emptying. Medications such as threo-chlorocitric acid or its derivatives, which inhibit gastric emptying, may increase satiety directly and via intestinal hormones (4).

**Miscellaneous**

_Human chorionic gonadotropin (HCG)._ The treatment of obesity with diet and injections of HCG has been proposed for more than 30 years. There have been three double-blind, placebo-controlled parallel studies (27) comparing injections of HCG and placebo added to a low-calorie diet. In no instance was there a statistically significant improvement in the rate of weight loss during treatment with HCG compared with placebo. Thus, HCG is not effective in the treatment of obesity.

_Regional fat mobilization_. Lipolysis in human adipose tissue is stimulated by drugs that act on β-adrenergic receptors and is inhibited by drugs that act on α2-adrenergic receptors. These clinical observations suggested that it might be possible to mobilize fat locally by β-adrenergic stimulation or inhibition of α2-adrenergic receptors. This possibility has received tentative support by finding that local injection of isoproterenol, a β-adrenergic agonist, into one thigh of women on a diet increased the rate of fat loss from the treated thigh. Local applications of a cream containing aminophylline to increase β-adrenergic–like effects of yohimbine, an α2-adrenergic blocking drug, also increased the mobilization of fat from the treated thigh. The possibility of treating regional fat deposits by topical means has thus been proposed and awaits further testing (28).

**Conclusions**

In spite of the daunting regulatory hurdles and widespread negative attitudes toward obesity, quite a few potentially useful agents are under development and this may lead to changes in attitude and changes in methods of treatment (Table 3). Demonstration of a role for the sympathetic nervous system in regulation of energy expenditure has led to development of thermogenic drugs by several companies. At the present time, a clinical trial is available for only one such compound. Additional clinical trials with thermogenic drugs are awaited. These drugs are of particular interest because they can modify the distribution of energy between fat and protein. They are biologically similar to the effect observed with physical activity, i.e., they increase muscle and decrease fat stores.
Additional drugs are under development, including centrally acting metabolites and drugs that affect lipid digestion. Comparative studies of drugs vs behavioral treatment have been carried out for fenfluramine but are needed for other agents. Most of the currently available drugs are safe and are underutilized because of perceptual, regulatory, and research barriers. Development of new drugs and use of old ones is hampered by public, professional, regulatory, research, and legislative barriers. Conceptually, all forms of experimental obesity can now be treated by drugs. Only more research and an improved regulatory environment will bring their potential value to the public.

References