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USE OF DRUGS IN THE TREATMENT OF OBESITY

Richard L. Atkinson
Departments of Medicine and Nutritional Sciences, University of Wisconsin, Madison, Wisconsin 53706-1571; e-mail: RLA@medicine.wisc.edu

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ABSTRACT

Obesity has become an epidemic in the United States and in many other countries of the world. Obesity is a chronic disease, not a failure of willpower. Diet, exercise, and behavioral modification of lifestyle are rarely successful over the long term. Medications have been used sparingly, because of concerns about addiction and ineffectiveness, but used chronically, obesity drugs are effective. The two main categories of obesity drugs are centrally active adrenergic and serotonergic agents. These drugs reduce appetite, enhance satiety, and increase energy expenditure. Use of single agents produces modest weight loss and use of combinations increases loss, but few patients reach their goal weight. Co-morbidities associated with obesity resolve or are reduced in severity with weight loss. Adverse events of major concern are changes in brain biochemistry and primary pulmonary hypertension. Published guidelines for use of obesity medications recommend they be used only for medically significant obesity.

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BACKGROUND

Obesity is the most common disease in the United States and in much of the world. The 1990 National Health and Nutrition Evaluation Survey (NHANES), carried out by the US Government, demonstrated that one third of the adult population and over 20% of the children in the United States have medically significant obesity (39). This is an increase in the prevalence of obesity of more than 30% in the decade between 1980 and 1990. Obesity produces numerous co-morbidities, such as diabetes mellitus, hypertension, dyslipidemia, sleep apnea, cancer, and gall bladder disease, all of which contribute to the increase in mortality with obesity, particularly in younger individuals (12, 31, 53, 63). It has been estimated that more than 300,000 people die each year from obesity-related diseases (47, 66).

In the past, obesity has not been considered a chronic disease. Rather, it has been attributed to a failure of willpower or a lack of self-discipline. Recent research suggests that genetic factors are responsible for 20–50% of the variance of obesity in the general population (10, 11), and biochemical and metabolic differences between obese and lean humans have been well documented (10–12, 31, 63, 64). Although this research demonstrates that obesity is a disease of altered physiology and biochemistry, the psychological aspects of obesity have outweighed physiological and biochemical aspects in determining treatment. For many years, obesity treatment focused almost exclusively on the use of behavioral techniques to reduce calorie and fat intake and to increase exercise. Numerous strategies for behavior modification were promoted, and although initially successful, this form of therapy rarely is successful over the long term. In published studies from academic centers, only about two thirds of weight loss is maintained at one year, and the five-year success rate often is less than 5%, though there are exceptions (2, 38, 52, 69, 73).

Despite the poor success rate of behavioral therapy for obesity, physicians have been reluctant to use pharmacological therapy (13). Early drugs developed for the treatment of obesity, such as dexamphetamine and methamphetamine,

were associated with physiological dependence (13). Newer variations with minimal or no abuse potential were developed, but physicians continued to use first-generation drugs, often prescribing them in combinations with excessive doses of thyroid hormone, diuretics, and even digitalis preparations. The US Congress held hearings on the abuse of these drugs. As a result, both the federal government and many state governments placed severe restrictions on their use. Approval for treatment with obesity drugs was limited to 12 weeks by the US Food and Drug Administration (FDA), and many states prohibited their use completely. The negative publicity and government restrictions resulted in a marked suspicion of obesity drugs on the part of physicians, other health care professionals, and the general public. Few insurance companies pay for obesity drugs, and the impression has persisted until recently that obesity drugs are ineffective and dangerous.

The problem was compounded by the lack of research, sponsored by either the government or private industry, on pharmacologic treatments for obesity. There was a 23-year hiatus between approval by the FDA of fenfluramine and mazindol (1973) and approval of dexfenfluramine (1996). Despite the negative atmosphere surrounding obesity drugs, recent research has begun to change perception of them. The realization has come slowly to clinicians, and lately to the general public, that since obesity is a chronic disease with specific genetic, physiological, and biochemical differences, it should be treated the same as other chronic diseases. Most chronic diseases are treated with drugs. Most drugs must be used long-term, usually lifelong.

In 1992, Weintraub (70) reported that obesity drugs reduced body weight and complications of obesity for up to 3.5 years. Coupled with discoveries in several animal models of a genetic basis for obesity (17, 18, 33, 51, 76), these studies altered the perception of pharmacologic treatment of obesity and led to a rapid expansion of research on obesity drugs and to a dramatic increase in their long-term use.

PHYSIOLOGICAL MECHANISMS OF ACTION OF OBESITY DRUGS

Obesity is the storage in the body of excess energy as fat. In order to reduce body fat, there must be a period of negative energy balance. This must be accomplished either by a reduction in food intake or by an increase in energy expenditure. Pharmacologic agents act by different mechanisms on the energy-balance equation (Table 1).

Reduction of Energy Intake

Reduction of energy intake may occur in several ways. Most obesity drugs are thought to reduce appetite or hunger, so food-seeking behavior is reduced

Table 1 Obesity drugs: potential mechanisms of action

Reduce energy intake
Decrease hunger and/or appetite
Increase satiety
Decrease fat and/or carbohydrate preference
Reduce nutrient absorption
Increase energy expenditure
Stimulate physical activity
Tremor
Spontaneous physical activity
Increase metabolic rate
Increase resting metabolic rate
Increase thermogenesis with eating, cold, exercise

(32, 41, 62). However, there also is evidence for increased satiety, resulting in reduced amounts of energy being consumed in a meal. There is limited evidence that obesity drugs may alter dietary preference. Studies by Wurtman et al (74) suggested that serotonin agonists may reduce cravings for carbohydrate, and Blundell et al (7) reported that dexfenfluramine may reduce preference for dietary fat. If the total quantity of food intake remains unchanged, reduction of the proportion of calories as fat will reduce energy intake. Also, Boozer et al (8, 9) have shown that in rats, equicaloric alterations in the percentage of calories as fat in the diet may have profound effects on body composition, which suggests differences in energy metabolism with dietary fat.

Another method of reducing energy intake is by reduction of absorption of nutrients from the GI tract, in effect producing malabsorption. As described below, two drugs are available that block absorption from the GI tract by binding or inactivating enzymes that digest fat or carbohydrate (6, 23, 24).

Increase in Energy Expenditure

Obesity drugs may increase energy expenditure in two ways: by stimulating an increase in activity levels, or by increasing metabolic rate directly. Some patients complain of tremors, particularly during the initial phase of treatment with certain pharmacologic agents (20, 67). Tremors are muscle contractions and require energy expenditure. Anecdotally, patients report an increase in willingness to exercise and increased comfort when active, but there have been no studies that have documented this. Most studies include behavioral therapy that focuses on increasing the patient's level of activity, so the independent contribution of medications is difficult to determine.

Numerous studies have evaluated the effects of obesity drugs on metabolism. This literature is controversial, but some animal and human studies suggest that some obesity drugs may increase energy expenditure by increasing the resting metabolic rate; others report increased dietary-induced thermogenesis (41, 68).

Levitsky & Troiano (41) reported that rats given fenfluramine had a normal resting metabolic rate but an exaggerated rise in energy expenditure after a meal compared with untreated control animals. Troiano et al (68) demonstrated a similar phenomenon in humans. However, other investigators have found no increase in either resting metabolic rate or in dietary-induced thermogenesis with fenfluramine or dexfenfluramine (58).

The combination of ephedrine and caffeine has been shown to increase energy expenditure, probably by stimulating beta-adrenergic receptors (42, 64). Stock et al (42, 64) demonstrated that beta-1 and beta-2 receptors were initially stimulated, but tachyphylaxis occurred rapidly. However, the chronic increase in metabolic rate suggested a continued stimulation of beta-3 receptors.

Theory of Altered Defense of Body Weight

Some authors advance the theory that obesity drugs may reduce the level at which body weight is defended. Keesey & Powley (37) have argued that animals and people have a "set point" around which weight is defended. Other authors suggest this is a "settling point" due to the confluence of numerous factors that affect body weight (26). There is no doubt that weight loss induced by dieting lowers metabolic rate in both animals and humans (37). It appears that treatment with obesity drugs reduces body weight, and this reduction is maintained at the lower level. Levitsky & Troiano (41) showed that animals initially decreased food intake and lost weight with fenfluramine or dexamphetamine, but that food intake returned to baseline without a regain in body weight. This phenomenon also is seen in patients and animals after intestinal bypass or ileal transposition surgeries (3).

CATEGORIES OF OBESITY DRUGS AND BIOCHEMICAL MECHANISMS OF ACTION

Maintenance of energy balance is so critical to survival that there are many redundant mechanisms that influence food intake and energy expenditure (14). Numerous areas of the brain have been shown to participate in the regulation of energy balance, and they respond to different neurotransmitters. Some of the more important areas are listed in Table 2. The only drugs approved for the treatment of obesity in the United States act on two of the more important neurotransmitters systems to regulate energy balance: the centrally active adrenergic and serotonergic systems.

Centrally Active Serotonergic Agents

Fenfluramine and dexfenfluramine are the only two serotonergic agents approved by the FDA (Table 3). Fenfluramine is the racemic mixture of D- and L-fenfluramine. Dexfenfluramine is the active agent that produces weight loss.

Table 2 Some areas of the central nervous system involved in regulation of food intake and energy expenditure

Arcuate nucleus
Area postrema
Dorsomedial hypothalamus
Dorsal brachial nucleus
Lateral hypothalamus
Nucleus acumbens
Nucleus tractus solitarius
Paraventricular nucleus
Suprachiasmatic nucleus
Ventromedial hypothalamus

These agents act by stimulating the secretion of serotonin from the nerve terminals of critical nuclei of the brain, but they also prevent reuptake of serotonin in the neural clefts. Fluoxetine and sertraline are antidepressant agents that are not approved for obesity, but they have been shown to produce weight loss in humans or animals and have been used by clinicians for obesity. They are thought to act exclusively as serotonin reuptake inhibitors. About 15 different serotonin receptors have been identified (5), and the differences in effectiveness of the fenfluramines versus other serotonergic agonists may be determined by which receptors are bound. Weight loss with fluoxetine is approximately similar to that produced by D-fenfluramine, but in contrast to D-fenfluramine, the loss is only temporary (28). Weight loss reaches a maximum at about six

Table 3 Current pharmacologic agents used for obesity and their DEA schedule category[a]

Catecholaminergic drugs		Serotonergic drugs	
DEA no.	Generic name[b]	DEA no.	Generic name
II	Amphetamine (Dexedrine)	IV	Fenfluramine (Pondimin)
II	Methamphetamine (Desoxyn)	IV	Dexfenfluramine (Redux)
II	Phenmetrazine (Bontril)	NA	Fluoxetine (Prozac)
III	Benzphetamine (Didrex)		
III	Chlorphentermine		
III	Chlortermine		
III	Phendimetrazine (Plegine, Prelu-2)		
IV	Diethylpropion (Tenuate)		
IV	Mazindol (Sanorex, Mazinor)		
IV	Phentermine (Ionamin, Fastin, Adipex)		
OTC	Phenylpropanolamine (Dexatrim, Accutrim)		
NA	Ephedrine & caffeine (numerous names)		

[a]DEA, Drug Enforcement Agency; NA, not currently approved by the Food and Drug Administration for the treatment of obesity; OTC, over the counter.

[b]Trade name in parenthesis.

months, then there is a gradual regain. The one-year loss with fluoxetine is not significantly different from that with placebo.

Both fenfluramine and dexfenfluramine are currently listed as category IV controlled substances by the FDA and the US Drug Enforcement Agency (DEA). Drugs that are scheduled by the DEA are presumed to have abuse or addictive potential. However, animal studies show that fenfluramine and dexfenfluramine do not have reinforcement potential (30). Testimony at a combined FDA-DEA meeting on these agents on September 29, 1995, confirmed that there is essentially no potential for addiction and that these two drugs are rarely the targets of abuse.

Centrally Active Adrenergic Agents

There are a variety of centrally active adrenergic agents that are approved by the FDA and available in the United States for the treatment of obesity (Table 3). These adrenergic agents either stimulate secretion of norepinephrine from central nervous system (CNS) nerve terminals or inhibit its uptake, thus leading to actions on food intake and energy expenditure.

The drugs shown in Table 3 in DEA schedule II are not routinely used or are used only in extremely rare circumstances by responsible physicians. These include dexamphetamine, methamphetamine, and phenmetrazine. These drugs have significant abuse potential and do not produce significantly greater weight loss than do less addictive agents (62). Schedule III drugs include benzphetamine, chlorphentermine, chlortermine, and phendimetrazine (Table 3) and are thought to have less abuse potential, but they are not used by most physicians for treating obesity.

Adrenergic drugs in DEA schedule IV include phentermine, diethylpropion, and mazindol; these are the adrenergic drugs most used by physicians in the United States to treat obesity. All three of these drugs have minimal addiction or abuse potential (30), and the popularity of phentermine over the other two is due primarily to the publicity of the Weintraub regimen (70). Griffiths et al (30) demonstrated in non-human primates that diethylpropion had a somewhat higher reinforcement potential than did phentermine. Phentermine and diethylpropion stimulate norepinephrine from CNS nerve terminals, and mazindol acts predominantly as a reuptake inhibitor. Silverstone (62) concluded that all of the drugs in this category produce approximately the same amount of weight loss.

Experimental Drugs or Drugs Not Currently Approved

A list of drugs not currently approved by the FDA is listed in Table 4. Sibutramine blocks reuptake of both norepinephrine and serotonin in nerve terminals and is under consideration by the FDA for approval for use in obesity. Clinical trials show weight losses of about 7–10 kg (15, 57), but the drug produces less decrease in blood pressure of hypertensive patients than does a placebo with

Table 4 Experimental or potential pharmacologic agents for the treatment of obesity[a]

Currently approved or under consideration by the FDA or in clinical trials
Combined adrenergic and serotonergic: Sibutramine[b]
Drugs affecting absorption: Orlistat[b]; Acarbose[c]
Potential future agents
Gut peptides: e.g. CCK, enterostatin
Opioid antagonists: e.g. naltrexone
Neurotransmitter agonists and antagonists: e.g. CRH, anti-galanin, anti-NPY
Thermogenic agents: e.g. β-3 agonists
Growth hormone, growth factors: e.g. GH, IGF-I
Lipid oxidizing agents: e.g. RO-22-0654
Gene products: e.g. leptin, GLP-1

[a]FDA, Food and Drug Administration; CCK, cholecystokinin; CRH, corticotropin releasing hormone; NPY, neuropeptide Y; GH, growth hormone; IFG-I, insulin growth factor 1; GLP-1, glucagon-like peptide 1.

[b]Currently under consideration for FDA approval.

[c]FDA approved for diabetes but not for obesity treatment.

a comparable degree of weight loss (57). Blood pressure may rise slightly in normotensive patients, as does pulse rate (57). These side effects have raised concern and have led to recommendations that patients should be carefully followed early in the course of treatment and that medications should be stopped if weight loss is not satisfactory or if blood pressure rises.

Orlistat reduces absorption of fat by binding to lipase in the intestine and by inhibiting its action (23, 24). Clinical trials have recently been concluded in the United States, but there is little data published in the literature on orlistat. Orlistat has an advantage over the centrally active adrenergic and serotonergic agents listed above because it acts peripherally and is not expected to have any adverse effects on cardiovascular function. Side effects include intestinal gas, cramping, and diarrhea, which may make it unacceptable to some patients.

Acarbose is an alpha-glucosidase inhibitor that reduces digestion of complex carbohydrates, allowing them to pass unabsorbed into the large intestine (6). The appearance of undigested complex carbohydrates in the colon is associated with increased intestinal gas, flatulence, abdominal pain, and diarrhea. Acarbose is approved in the United States for treatment of diabetes, but its effects in studies for the treatment of obesity were disappointing. It is not an adequate weight-loss agent.

Gut Peptides, CNS Neurotransmitter Agonists and Antagonists, Thermogenic Agents

Numerous gut peptides have been shown to inhibit food intake and are candidates as obesity drugs (14). A comprehensive review of gut peptides is beyond

the scope of this chapter, but a sample of peptides that have attracted interest as potential obesity drugs is shown in Table 4. Since gut peptides are subject to digestion in the GI tract, they may need to be given as injections unless carrier molecules can be identified. This may limit their usefulness.

Cholecystokinin (CCK) is the gut peptide that has been the best studied in humans. Several studies demonstrate that CCK can reduce food intake acutely (14, 72). Longer-term studies in animals do not give cause for optimism, however, as it appears that animals adapt to repeated administration (72).

Enterostatin is of particular interest: not only has it been shown to reduce total energy intake, it also specifically reduces preference for dietary fat (50). Enterostatin is effective when injected into the cerebrospinal fluid (CSF) of animals, but intravenous injections are much less effective. Recent studies suggest that enterostatin may be effective if given orally (48). This suggests that there may be receptors on enterocytes. The mechanism of signaling the CNS from the GI tract is unknown.

Growth hormone, insulin growth factor-1, and other growth factors have been proposed as potentially useful in treating obesity or in increasing lean body mass (14, 56). Long-term treatment with growth hormone may be associated with the development of acromegaly and diabetes mellitus, so the utility of GH is limited. The increase in lean body mass and decreased fat mass associated with GH and other growth factors may be due to increased lipolysis and fat oxidation, so research into these types of agents continues.

Most CNS neurotransmitters are effective only when injected into the CSF or into specific nuclei of the brain. CCK is effective when injected into the CSF or CNS, so it has a dual action as a gut peptide and CNS neurotransmitter. Corticotropin releasing hormone (CRH) has been shown to reduce food intake and cause body weight (14). Two CNS neurotransmitters, galanin and neuropeptide Y (NPY), have attracted particular attention. Galanin stimulates fat intake when injected into the paraventricular nucleus of the hypothalamus (40). NPY is one of the most potent known stimulators of food intake when injected into the hypothalamus or CSF (40). Several companies are attempting to identify antagonists to these two substances with the hope that they will produce long-term reduction of energy intake.

Thermogenic agents represent a potentially promising area of investigation. Animal studies of candidate drugs demonstrated dramatic reductions in fat mass and increases in lean body mass, accompanied by increases in metabolic rate (75). These drugs were thought to act by binding to beta-3 adrenergic receptors of atypical adrenergic receptors and, thus, increase metabolic rate. However, when these agents were used in humans, it became apparent that animal beta-3 receptors are different from human beta-3 receptors, and these agents were ineffective. Newer research has identified atypical adrenergic receptors with

the properties of animal beta-3 receptors, and work on compounds that may be active in humans is ongoing. Some of the side effects of beta-3 agonists have been an elevation in blood pressure and pulse rate, and some fears of cardiac arrhythmias. These effects may be due to nonselective stimulation of beta-1 and beta-2 adrenergic receptors.

There have been a few studies of the combination of ephedrine with caffeine and/or aspirin for obesity (20, 67). It appears that this combination results in chronic stimulation of the beta-3 adrenergic system, with the attendant increase in lean body mass and decrease in fat mass (20, 42, 64, 67). Ephedrine may be extracted from the Chinese plant ma huang, caffeine may be extracted from coffee beans, and acetosalicylic acid (aspirin) may be extracted from willow bark. Since such extracts may be marketed as "supplements" in the United States and are subject to minimal FDA oversight, sales of varieties of this combination are currently booming. The FDA and Federal Trade Commission have become concerned and issued warnings because a number of people have had cardiac events or even died while taking these compounds.

Ephedrine stimulates norepinephrine secretion, which binds to a variety of alpha and beta receptors in peripheral nerve terminals. Caffeine appears to act in two ways to delay degradation of norepinephrine. It inhibits adenosine degradation of norepinephrine in the neural cleft, and it inhibits phosphodiesterase in the postsynaptic neuron. Norepinephrine acts via cyclic AMP, and phosphodiesterase metabolizes cyclic AMP. Aspirin inhibits the activity of prostaglandins that degrade norepinephrine in the neural cleft. Thus, the end result of treatment with these three agents is a prolonged increase in norepinephrine activity. During the initial phase of treatment with these agents, norepinephrine stimulation of beta-1 and -2 receptors produces increases in heart rate and blood pressure and elevates serum insulin levels, occasionally worsening glucose intolerance or diabetic control. Some patients report a tremor. However, tachyphylaxis occurs fairly rapidly, and over approximately one month, these symptoms resolve (42, 64). Tachyphylaxis does not appear to occur with beta-3 receptors, and there is a continued increase in metabolic rate for periods of up to a year (42, 64). Lipolysis is enhanced and lipogenesis is decreased.

Gene Products

The discovery of the gene defect responsible for obesity in *ob/ob* mice and the subsequent identification of the *ob* gene protein generated intense publicity (17, 33, 51, 76). This was rapidly followed by discovery of a defective receptor for *ob* gene protein, causing the defect identified as the *db/db* mice and the Zucker obese rat. The *ob* gene product was named leptin, and there is hope that leptin will be useful for the treatment of obesity (76). Leptin promotes weight loss in *ob/ob* mice, in normal mice, and in mice made obese by high-fat diets

(17, 33, 51). The initial hypothesis upon discovery of leptin was that humans—similarly to the *ob/ob* mouse—would be deficient in it. This optimism was dampened by the findings that most obese humans have elevated levels of leptin (19), and some investigators have speculated that leptin will not be effective in reducing body weight in obese humans. However, the findings that rodents made obese by being fed high-fat diets have high leptin levels and still respond to leptin injections suggests that there may be leptin resistance similar to insulin resistance in Type II diabetes. Since much human obesity is exacerbated by high-caloric, high-fat diets, there is hope that with sufficient doses of leptin, humans will achieve weight loss. Phase I clinical trials have started, but there are no data on leptin's effectiveness in humans.

PRACTICAL ASPECTS OF INTEGRATING DRUGS INTO OBESITY TREATMENT

Who Should be Treated with Obesity Drugs

Several sets of guidelines have been advanced to help clinicians select appropriate patients for treatment (49, 54, 60, 66). The National Institutes of Health (NIH) National Task Force on the Prevention and Treatment of Obesity recommends against general physicians prescribing long-term use of obesity drugs until additional research has been performed (49). The FDA released guidances for the pharmaceutical industry for the types of studies necessary to obtain approval for new obesity drugs. These guidances suggested that obesity drugs may be used by individuals with a body mass index (BMI) of 30 kg/m^2 without co-morbidities and a BMI of 27 kg/m^2 with co-morbidities. The North American Association for the Study of Obesity convened a broad-based group consisting of academicians, clinicians, industry representatives, and representatives from several government agencies—including the NIH, FDA, Federal Trade Commission, and Health Care Financing Administration—that developed guidelines for the use of obesity drugs (54). These guidelines recommended that drugs might be considered for individuals with a BMI of 27 kg/m^2 if no co-morbidities were present. Drugs may be considered for individuals with a BMI below 27 in the presence of co-morbidities after careful consideration of the risks and benefits of drug use. Shape Up America! and the American Obesity Association (AOA) developed a comprehensive set of guidances for physician treatment of obesity that includes recommendations for obesity drugs (60). These guidances follow the FDA model of a BMI of 30 for individuals without co-morbidities and a BMI of 27 for those with co-morbidities, but they allow a greater leeway for physicians to assess individual patients and come to a rational decision based on the individual risk factors and risk/benefit ratio.

Table 5 Contraindications or cautions to the use of obesity drugs[a]

Pregnancy or lactation
Unstable cardiac disease
Uncontrolled hypertension
Unstable severe systemic illness
Unstable psychiatric disorder or anorexia
Other drug therapy, if incompatible (e.g. MAO inhibitors, migraine drugs)
Closed-angle glaucoma (caution)
General anesthesia (absolute contraindication, except emergencies)

[a]MAO, Monamine oxidase inhibitors.

The AOA-Shape Up America! document (60) suggested that obesity drugs be restricted to adults aged 18 and above and listed conditions that are contraindications or cautions to their use (Table 5). Due to the limited research on long-term use of obesity drugs, it was recommended that these agents not be used by patients with unstable medical or psychological conditions. Closed-angle glaucoma may be exacerbated by both adrenergic and serotonergic agents, so this condition requires careful follow-up if obesity drugs are used. Age above 65 years is a caution (4). Obesity drugs generally do not interact negatively with other drugs, with some notable exceptions. Antidepressant agents, including tricyclic and selective serotonin reuptake inhibitor drugs, should be used only with caution, and monamine oxidase inhibitors are absolutely contraindicated because of the possibility of excess serotonin activity in the CNS.

How Should Obesity Drugs Be Used

There is growing sentiment among clinicians and scientists who prescribe obesity drugs that, in individuals who have significantly severe obesity to warrant the use of drugs, long-term, including life-long, use may be necessary (60). The previous recommendations by pharmaceutical companies and the FDA,

Table 6 Obesity drugs: dosage regimens[a]

Drug	Initial (mg/day)	Maximum (mg/day)
Dexfenfluramine	15	30
Fenfluramine	10–20	60
Diethylpropion (CR)	75	75
Mazindol	1	3
Phentermine HCL	8–19	37.5
Phentermine resin	15	30
PPA	75	75

[a]PPA, Phenylpropanolamine.

that obesity drugs be used for only 12 weeks, has been abandoned. Because the initial period of treatment with obesity drugs is associated with a high number of side effects, a stepped-dose approach has been recommended (60, 66). Table 6 lists initial and maximum dosages for the most commonly used obesity drugs.

RESULTS OF TREATMENT

Studies with Single Drugs

The vast majority of clinical trials with obesity drugs have involved the use of single agents for short periods of time. Scoville (59) reviewed the results of over 200 studies of single agents and concluded that all the agents available at that time produced essentially comparable results. The average additional weight loss above the placebo-treated control groups was about 0.5 lb per week (59). Silverstone (62) reached similar conclusions when comparing short-term results from different agents.

Unfortunately, few long-term studies have evaluated any obesity drug for longer than a year. Goldstein & Potvin (27) surveyed the literature and found only nine studies that had followed subjects for a year or more (Table 7). As seen in Table 7, with the exception of fluoxetine, longer-term weight loss ranged from about 5 kg to about 14 kg, and most of the drugs produced better weight loss than a placebo did. Placebo weight losses in several studies were very good, demonstrating that the studies were not simple tests of drug versus placebo: Both groups underwent standard obesity therapy with diet, exercise, and behavioral therapy.

Table 7 Long-term clinical trials with obesity drugs[a]

Obesity drug	One-year weight loss	
	Placebo	Active agent
Diethylpropion (61)	−10.5	−8.9
Mazindol (25)	−10.2	−14.2
Mazindol (36)	—	−12.0
Fenfluramine (35)	−4.5	−8.7
Dexfenfluramine (32)	−7.2	−9.8
Dexfenfluramine (65)	−2.7	−5.7
Dexfenfluramine (45)	−4.6	−5.2
Fluoxetine (44)	+0.6	−13.9
Fluoxetine (21)	−4.5	−8.2
Fluoxetine (28)	−1.5	−2.3

[a]Adapted from Goldstein & Potvin (27). References in parentheses.

Guy-Grand et al (32) reported the results of the year-long INDEX study of dexfenfluramine in several centers in Europe. Dexfenfluramine produced a weight loss of 9.8 kg at one year versus a loss of 7.2 kg with a placebo. Mean one-year weight loss was about 11% of initial body weight. More than twice as many subjects lost at least 10% of initial body weight on dexfenfluramine as did those on placebo. About 60% of the subjects who started the year completed one year of drug treatment versus only about 50% of subjects on a placebo. Side effects were modest.

Mazindol produced the largest weight losses (14.2 kg) with a single agent in the review by Goldstein & Potvin (27), but the large loss in the placebo group (10.2 kg) suggests that the behavioral component was quite strong in this study.

Fluoxetine produces excellent weight loss over the first six months of treatment (21, 28, 44), although weight regain occurs thereafter and one-year weight was not different between the placebo and the experimental groups in 8 of 10 studies reported in a summary paper by Goldstein et al (28). Two sites, Marcus et al (44) and Darga et al (21), included a strong behavioral program and were able to obtain significant weight loss at one year.

Studies with Drug Combinations

Only three combinations of drugs have been reported in full publications: phenylpropanolamine-benzocaine, ephedrine-methylxanthines-aspirin, and fenfluramine-phentermine (4, 20, 29, 67, 70, 71). Phenylpropanolamine is an adrenergic agent that is sold over the counter in the United States and that has no reinforcement potential in animals (30). It produces modest weight loss when used alone (29). Benzocaine is a local anesthetic agent contained in some over-the-counter weight reduction aids. The rationale for its use is to anesthetize the taste buds and thus reduce food intake. In the only publication using this combination, Greenway et al (29) found that in an eight-week trial, weight loss was similar in the drug and the placebo groups.

The combination of ephedrine and caffeine, with or without aspirin, produces results that are among the best of any drug regimen reported (20, 67). Toubro et al (67) compared placebo, ephedrine alone, caffeine alone, and the combination of ephedrine and caffeine over a period of 24 weeks in 180 subjects. The combination of ephedrine and caffeine produced weight loss of about 16 kg at 24 weeks. Of the initial 180 subjects, 99 were followed for another 26 weeks in an open-label study. Weight loss persisted for as long as the drugs were given. Daly et al (20) treated six subjects in an open-label study for periods of up to 26 months and noted a persistent, modest weight loss.

The combination of fenfluramine, a serotonin agonist, and phentermine, an adrenergic agonist, was first reported in 1984 by Weintraub et al (71). Full doses of fenfluramine (120 mg/day) or phentermine (30 mg/day) were compared

with the combination of half-strength doses of each (60 and 15 mg/day, respectively). Weight loss among the groups was similar, but full doses of both fenfluramine and phentermine produced significantly more side effects than the placebo did. In contrast, side effects with the combination were not different from the placebo. Weintraub et al (70) then performed a four-year follow-up study that generated an enormous amount of publicity and changed the perception of the use of drugs for obesity. A total of 121 subjects started treatment with either the combination or the placebo in a double-blind, randomized trial for an initial period of 34 weeks. All subjects received diet, exercise, and behavior modification throughout the study. Weight loss reached a plateau at about 25 weeks into the initial 34-week period. All patients were then treated with the combination in an open-label fashion, and at 60 weeks, a 15.8-kg weight loss persisted. Subjects who lost little weight during the first 34 weeks were increased to dosages of 120 mg/day of fenfluramine and 30 mg/day of phentermine resin, but they still did not respond. These data suggest that individuals who respond to this combination may be biochemically different from nonresponders, and that if patients fail to lose weight initially, continued treatment is not indicated.

This trial continued for four years, with periods of intermittent treatment for some subjects and continuous treatment for others. Discontinuation of drugs led to weight gain and reinstitution led to weight loss during the intermittent treatment phases. At about three years, subjects were randomized to drugs versus a placebo in a double-blind fashion. Subjects who were randomized to placebo gained weight. When all medications were terminated at about 3.5 years and all subjects were followed for 6 months off drugs, virtually all regained back to or near their baseline weights.

Side effects included dry mouth, fatigue, sweating, insomnia, and other sleep disturbances. In general, the side effects were tolerable and few subjects discontinued drugs for this reason. There were significant decreases in blood pressure at 34 weeks in this protocol, and serum lipid levels were assessed at two years. Serum cholesterol and triglycerides decreased by 34 weeks and continued to be lower at two years.

Atkinson et al (4) treated over 1300 subjects with phentermine and fenfluramine for periods of up to two years. They noted weight losses of about 16 kg that persisted for two years in subjects who continued on drugs. In patients with hypertension [systolic blood pressure (BP) of $\geq$140 mm Hg or diastolic BP of $\geq$90 mm Hg], systolic BP fell by 28 mm Hg and diastolic BP fell by 17 mm Hg. In patients with hypercholesterolemia (serum cholesterol of $\geq$200 mg/dl) or hypertriglyceridemia (serum triglycerides of $\geq$150 mg/dl), cholesterol levels decreased by 27 mg/dl and triglycerides decreased by 79 mg/dl, respectively (4).

Side effects reported by this group were more common than in the study by Weintraub (70). Dry mouth was the most frequent complaint, occurring in over 60% of patients. Fatigue, constipation, and sleep disturbances, including insomnia and vivid dreams, occurred in 10%–20% of patients. Short-term memory loss, an adverse event not reported by Weintraub (70), was reported by about 13% of patients. Seven patients discontinued the drugs or were taken off the drugs because of short-term memory loss or decreased mental acuity. Function returned to normal in all subjects. Weintraub noted in oral presentations that their subjects also had reported decreased mental acuity, but testing during a period of randomization to drugs or a placebo revealed no differences (M. Weintraub, personal communication). The studies by Atkinson et al (4) were open label, so there was no control group. Patients were given a follow-up sheet with a list of complaints, including short-term memory loss, so the frequency with which all side effects or adverse events were reported was likely to be higher.

Studies with fluoxetine and phentermine have been reported only in abstract form. Dhurandhar & Atkinson (22) reported that the combination of fluoxetine (20–60 mg/day) and phentermine hydrochloride (18.75–37.5 mg/day) produced significant weight losses that were similar to those produced by the combination of fenfluramine (20–60 mg/day) and phentermine HCL (18.75–37.5 mg/day). This study extended only to six months, so it is not possible to determine if the weight regain reported with fluoxetine after six months (28) will be prevented by the addition of phentermine.

CONCERNS ABOUT DRUG TREATMENT OF OBESITY

Dexfenfluramine is the only medication approved by the FDA for long-term use for obesity. However, the use of the combination of phentermine and fenfluramine has become so widespread that shortages of these drugs have occurred. Phentermine and fenfluramine were approved by the FDA for use for only 12 weeks, but changes in perceptions of obesity and obesity drugs after the publication by Weintraub (70) have led to suggestions that long-term use is indicated. Data from the limited studies by Weintraub (70) and Atkinson et al (4) suggest that for most people the side effects are quite modest. However, scientists in the field have expressed strong reservations about two potentially major adverse events: damage to the CNS and primary pulmonary hypertension.

Changes in the CNS

Changes in mental acuity and short-term memory loss have been reported in the literature, predominantly as anecdotes or in uncontrolled studies (4, 34). However, the frequency with which they are reported and data from the animal

literature raise concerns about alterations of CNS biochemistry. McCann et al and Ricaurte et al (46, 55) reported that squirrel monkeys and rodents treated with doses of dexfenfluramine from 4 to 40 times the postulated comparable human dose had depletion of serotonin in specific CNS areas for as long as 18 months after cessation of the drug. Human studies reported to the FDA by Interneuron, Inc, at hearings in July 1995 suggest that with doses of dexfenfluramine typically used by humans, the brain levels of dexfenfluramine as assessed by computed tomography scan are much lower than those seen in animals treated by McCann et al and Ricaurte et al (46, 55). In addition, Interneuron reported that the metabolites of dexfenfluramine in humans differ from those in animals and may also appear in the brain. The monkeys and rodents described by McCann et al and Ricaurte et al (46, 55) did not demonstrate any changes in function, including tests of memory and mental acuity.

Primary Pulmonary Hypertension

Primary pulmonary hypertension (PPH) is a rare disorder characterized by hyperplasia of the vascular endothelium of pulmonary blood vessels (40). In the 1960s, aminorex fumarate, a drug used for weight control in Europe, was reported to increase the risk of PPH (16). From a case control study, Brenot et al (16) suggested that D-fenfluramine and other obesity drugs increase the risk of PPH. A larger case control study, reported by Abenhaim et al (1), found 95 cases of PPH after screening 306 medical centers in Europe. The authors noted that particularly dexfenfluramine, but probably most anti-obesity drugs, are associated with an increase in the prevalence of PPH that may be as high as one in 20,000. This study has been attacked because of potential problems of patient selection bias and differential recall of use of obesity drugs between cases of PPH and the controls (43).

INTEGRATION OF OBESITY DRUGS INTO A COMPREHENSIVE OBESITY TREATMENT PROGRAM

Obesity drugs are only a part of a comprehensive program that includes diet, exercise, increased activity, and alteration of behavior to attain a healthy lifestyle (60). Few patients treated with drugs reach their goal weight and almost none reach “ideal” weight (4). Because obesity is a chronic disease, education of patients is critical. Education requires a significant commitment of time, and physicians rarely have sufficient time to accomplish the necessary degree of education. Several guidelines suggest that obesity treatment be conducted by a health care team that includes a physician and one or more allied health professionals, such as a dietitian, nurse, exercise physiologist, psychologist, or counselor (54, 55, 60, 66).

SUMMARY AND CONCLUSIONS

Obesity is a chronic disease that requires lifelong treatment. Experience with long-term use of obesity drugs is limited, but early data suggest that drugs improve the outcome of standard therapy. There are insufficient data to assume that treatment with these drugs for the long term is safe or efficacious. Weight loss usually is modest with obesity drugs, but there are significant improvements in co-morbidities of obesity. Two areas of major concern are the possibility that obesity drugs may produce decreases in mental acuity, presumably from biochemical changes in the CNS, and in primary pulmonary hypertension, which has been linked to obesity drugs by retrospective studies or anecdotal reports that need additional confirmation. Obesity drugs must be used with caution and administered only to patients with medically significant obesity. Careful follow-up and continuous assessment for efficacy and appearance of side effects are mandatory.

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