Chapter 5

Drug Treatment of Obesity

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Over the past 10 years research has uncovered a myriad of genes and gene products that have tremendous influence on the metabolic processes governing weight. A better understanding of the physiology of energy conservation and expenditure, appetite, satiety, the fat cell, regional fat deposition, and nutrient partitioning has opened doors that should lead to new approaches to the treatment of obesity (1–4). The importance of this research cannot be overstated. There was a 50% increased incidence of obesity in the United States between 1980 and 1994 and by the end of 1994, 22.5% of the population was obese [body mass index (BMI) $\geq 30\,\mathrm{kg/m^2}$] and 55% of the total population was overweight (BMI $\geq 25\,\mathrm{kg/m^2}$) (5,6).

The multitude of comorbid conditions that are caused by or associated with obesity is daunting: type 2 diabetes, cardiovascular disease (including atherosclerosis, fatty myocardium with arrhythmias and sudden cardiac death) (7–9), hypertension, gastrointestinal disturbances (fatty liver which may progress to cirrhosis (10), hiatal and abdominal wall hernias (11,12) and gall bladder disease), precipitation or aggravation of arthropathy of weight-bearing joints,

central nervous system abnormalities (papilledema, increased intracranial pressure) (13), renal diseases which may progress to nephrosis (14,15), respiratory failure secondary to restrictive pulmonary disease (Pickwickian syndrome, right-sided heart failure), and/or aggravation of obstructive lung disease as well as sleep apnea, with its associated pathology. Soft-tissue infections, varicose veins, ulcerations, intertrigo and acanthosis nigricans are seen with increased frequency in the obese. Certain coaguolopathies, such as hyperfibrinogenemia, may be present with obesity (7). Postmenopausal breast cancer, gall bladder and genitourinary cancers and colon cancer are also more common (16,17).

Endocrinopathies associated with obesity include hypothyroidism, hyperadrenalism, polycystic ovary syndrome, hyperinsulinemia, hypogonadism, growth hormone deficiency, and pituitary dysfunction. Complications of surgery and pregnancy are increased with obesity (18,19). The psychosocial and work-related morbidity of this disease is incalculable (16,17).

Obesity is a serious illness. Despite the fact that our present approach has had limited success in coping with it, there is light at the end of the tunnel. The unraveling and better understanding through research of the multiple complex interreactive factors responsible for this disease may enable us to discern which factor or factors lead to a specific phenotype or an individual's presentation of obesity. This should allow more specifically directed therapy.

Physicians, in general, have been reluctant to prescribe medications for the treatment of this disease. A poor track record plus serious side-effects including the addictive or psychotic-inducing properties of the amphetamines, complications associated with some of the newer drugs (fenfluramine, dexfenfluramine) (20) and, most recently, phenylpropanolamine (PPA) (21) does not foster a great deal of confidence in drug treatment of a disease that many physicians still feel is solely related to a faulty lifestyle. For the most part, obesity has been treated with a calorie-restricted diet and "lose some weight and I'll see you next year". Encouraging increased physical activity, behavioral

modification, and short-term drug therapy have been added by a number of physicians and treatment centers. These approaches have led to significant short-term weight loss in some patients, but long-term results have been poor. Regaining weight after a significant weight loss is well recognized but not well understood. During the 40,000–50,000 years' existence of modern man, famine has been a major factor in determining longevity, or the lack of it. It is not surprising that humans have developed many genetically determined traits to help them maintain body weight, resist weight loss during food deprivation and regain weight rapidly when food supplies are replenished. Increase in neuropeptide Y (NPY), the neuropeptide that elicits feeding response (22) and decreases in triiodothyronine and catacholamine activity leading to reduction in metabolic requirements in response to calorie restriction (23) are just a few examples of such responses. The multiple and redundant mechanisms that guard against weight loss probably interfere with the outcome of various weight management approaches by resisting weight loss or promoting weight gain in an individual.

Obesity management is further complicated by the fact that obesity is not a single disease but an expression of metabolic abnormalities generated by multiple factors. Overweight and obesity present in many guises. Fat deposition and lean body mass are variable. These variables are a reflection of underlying genetic and adaptive physiologic changes preceding and coinciding with the development of obesity. Sclafani (24) has classified the etiology of animal obesity into nine different groups: obesity of neural, endocrine, pharmacologic, nutritional, environmental, seasonal, genetic, idiopathic, or viral origin. At present, a reasonable or financially feasible way to determine the contribution of various etiologic factors in an obese individual is not available. As research continues, and the factors that are responsible for obesity in an individual are better characterized, we can anticipate more specific individualized approaches to obesity treatment (25).

Our current armamentarium for treating obesity is limited. Historically, the clinical treatment of obesity has

been limited to a low-calorie low-fat high-fiber diet, an exercise regimen, and lifestyle behavior modification. It is estimated that many people who lose weight will regain most of the weight lost after 5 years. Although the lifestyle modification, diet, and exercise are most important for long-term weight maintenance and overall health, obese patients may need additional help. Admittedly, pharmacologic treatment of obesity is in its infancy, but research has developed some new and useful drugs that should help with the struggle to control weight. Before we discuss these, it is paramount to re-emphasize that the lifestyle change is the most important component in weight management. Without it, long-term success is highly unlikely.

In this review, we discuss the pharmacologic treatment of obesity, including a discussion of recently approved drugs, those still available, and others that may soon become available. It should be emphasized that in mainstream health care circles, antiobesity drugs should be regarded as supplements and not substitutes for the patient's effort at lifestyle change to improve diet choices and increase physical activity.

ROLE OF DRUGS IN WEIGHT MANAGEMENT

The goal of drug treatment is to achieve a period of negative energy balance followed by a balance of energy intake and output with minimal adverse effects. Patients frequently achieve the initial negative energy balance but it is too often followed by a period of positive energy balance. This is, among other things, secondary to the physiologic changes that take place with the initial weight loss and may lead to resistance of further weight loss. It has been documented that exercise may partially ameliorate some of this problem with greater sustained weight loss for 1 year in exercisers (26,27). Negative energy balance can be obtained by decreased energy intake or increased energy expenditure, or a combination of both. As the medications are discussed, the mechanisms of action are noted regarding the effect on food intake, alteration of metabolism or increased energy expenditure.

For the most part, obesity drugs used in the recent past are associated with weight loss for the first 6 months of treatment and then there is a plateau or resistance to further weight loss (28,29). There is a gradual weight regain if the drugs are withdrawn (28). Present medications have a relatively narrow therapeutic target compared to all the compensatory changes that the body can bring to bear in maintaining or increasing body weight when it is lost.

The ideal drug that effectively produces fat loss in an obese individual, prevents regain, and has no side-effects is not yet available. The response of an individual to currently available obesity drugs cannot be predicted. By profiling patients and evaluating their response to a specific drug, we may be better able to determine which type of drug would benefit which type of obese patient in the future.

MECHANISMS OF ACTION OF OBESITY DRUGS

Obesity drugs may act in one or more of the following ways.

1. Reduction in energy (food) intake.
2. Increase in energy expenditure.
3. Reduced absorption of ingested calories.
4. Shifting of nutrient partitioning from body fat mass to lean body mass.

A description follows of various mechanisms employed by different drugs used for weight management (Table 5-1).

Reduction of Energy Intake

Reduction of energy intake may occur in several ways. Most antiobesity drugs are thought to reduce appetite or hunger, so food-seeking behavior is reduced (30–32). However, increased satiety, resulting in reduced amounts of energy being consumed in a meal, or altered dietary preference is also possible. It has been shown that serotonin agonists may reduce cravings for carbohydrate (33) and dexfenfluramine may reduce preference for dietary fat (34). If the total

Table 5-1 Drugs that Reduce Energy Intake

Drug Group	FDA Approved	Duration	DEA Schedule	Trade Names	Dosage Form	Administration
CENTRALLY ACTING AGENTS						
Norepinephrine releasers						
Methamphetamine	Yes Warning box	Few weeks	II	Desoxyn	5, 10, 15	10 or 15 mg. In a.m.
Amphetamine	Yes	Few weeks	II	Dexedrine	5, 10, 15	5 mg b.i.d. to t.i.d.
Benzphetamine	Yes	Few weeks	III	Didrex	25–50	Initial dose: 25 mg q.d. Maximum dose: 25–50 mg
Phendimetrazine	Yes	Few weeks	III	*Standard release:* Bontril PDM Plegine X-Trozine *Slow release:* Bontril Prelu-2 X-Trozine	35	35 mg ac t.i.d.
Diethylpropion	Yes	Few weeks	IV	Tenuate Dospan	25, 75	25 mg t.i.d. 75 mg q.d.

Table 5-1 continues

Table 5-1 (*Continued*)

Drug Group	FDA Approved	Duration	DEA Schedule	Trade Names	Dosage Form	Administration
Norepinephrine reuptake inhibitors						
Phentermine	Yes	Few weeks	IV	*Standard release:*		19–37.5 mg q.d. in a.m.
				Adipex-P	37.5	15–30 mg/day 2h pc breakfast
				Fastin	37.5	19–37.5 mg/day 9 a.m.
				Obenix	30	15–30 mg/day 2h pc breakfast
				Oby-Cap	30	15–30 mg/day 2h pc breakfast
				Oby-Trim	30	15–30 mg/day 2h pc breakfast
				Zantryl		
				Slow release:	15, 30	(initial dose on left)
				Ionamin		
Phentermine	Yes	Few weeks	IV	*Standard release:*	37.5	19–37.5 mg q.d. in a.m.
				Adipex-P	30	15–30 mg/day 2h pc breakfast
				Fastin	37.5	19–37.5 mg/day 9 a.m.
				Obenix	30	15–30 mg/day 2h pc breakfast
				Oby-Cap	30	

Drug	Approved	Schedule	Duration	Trade name	Strength (mg)	Dosage
Mazindol	Yes	IV	Few weeks	Oby-Trim Zantryl *Slow release:* Ionamin	15, 30	15–30mg/day 2 h pc breakfast 15–30mg/day 2 h pc breakfast (initial dose on left) 15 mg/day ac breakfast (30 mg for less responsive patients)
		IV		Sanorex	1, 2	Initial dose: 1 mg q.d. Maximum dose: 1 mg t.i.d. w/meals
				Mazanor	1	Initial dose: 1 mg q.d. Maximum dose: 1 mg t.i.d. w/meals
Serotonin–Norepinephrine Reuptake Inhibitor						
Sibutramine	Yes	IV	Long term	Meridia Reductil	5, 10, 15	Initial dose: 10mg/day Maximum dose: 20 mg/day
PERIPHERALLY ACTING AGENTS						
Orlistat	Yes		Long term	Xenical	120 mg	120 mg t.i.d. w/meals

volume of food remains unchanged, reduction of the proportion of calories as fat will reduce energy intake.

Energy intake could also be reduced by reduction of absorption of nutrients from the gastrointestinal tract, in effect producing malabsorption, as described below.

Increase in Energy Expenditure

Obesity drugs may increase energy expenditure by stimulating an increase in activity levels or by increasing metabolic rate directly. Some patients complain of tremor, particularly during the initial phase of treatment with certain pharmacologic agents (35,36). Tremor is muscle contraction and requires energy expenditure. Anecdotally, patients report an increase in willingness to exercise and feel more comfortable when active, but this has not been clearly documented. Most studies include behavioral therapy that focuses on increasing activity, so the independent contribution of medications is difficult to determine.

Animal and human studies suggest that some obesity drugs may increase energy expenditure by increasing resting metabolic rate (RMR), whereas others report increased dietary-induced thermogenesis (DIT) (31,37–39). The combination of ephedrine and caffeine has been shown to increase energy expenditure, possibly by stimulating β-adrenergic receptors (37,38). Compared to the untreated control group, rats given fenfluramine had a normal RMR but an exaggerated rise in energy expenditure in response to a meal (31). Troiano et al (39) demonstrated a similar phenomenon in humans. However, other investigators have found no increase in either RMR or in DIT with fenfluramine or dexfenfluramine (40).

Decreased Absorption

Interfering with digestion and/or absorption of macronutrients results in reduced availability of calories from the ingested food. A drug could inhibit a digestive enzyme or bind to its substrate (nutrient) and inhibit digestion and/or absorption. Drugs that reduce the digestion of dietary carbohydrates and fats by inhibiting the digestive enzymes are available and are discussed below. Chitosan is postulated to

reduce dietary fat absorption by binding with the fat. Most of the side-effects of the drugs reducing digestion or absorption are caused by the increased amounts of undigested nutrients reaching the large intestines. Drugs currently available in this category do not act centrally and therefore may be safer.

Nutrient Partitioning

It is considered that reducing the amount of *de novo* fat synthesis from macronutrients would reduce body fat stores. Hydroxycitric acid, an ingredient in the fruit *Garcinia cambogia* is a potent inhibitor of citrate lyase. Citrate lyase is a key enzyme in *de novo* lipogenesis and inhibition of this enzyme is postulated to result in reduced fat mass and body weight. Results of the clinical trials with hydroxycitric acid for weight loss are discussed below.

CATEGORIES OF OBESITY DRUGS

Centrally Acting Obesity Drugs

Adrenergic Stimulation α-I, -II, β-I, -II, and -III adrenoreceptors all have an effect on food intake, satiety and/or metabolism. Inhibition of food intake can be achieved by agonists of α-I or β-II adrenergic receptors.

Amphetamine and methamphetamine are Drug Enforcement Agency (DEA) Schedule II drugs which are rarely used because of their abuse potential and the reported psychotic reactions. They are no more effective than potentially less abusive drugs of the same class. All the amphetamine-like drugs are stimulants, which may lead to problems with blood pressure, tremor, dry mouth, constipation, and insomnia. These drugs have an anorectic effect by modulating the noradrenergic neurotransmission and a probable addictive effect through dopaminergic transmission.

Benzphetamine, phendimetrazine, chlorphentermine, and chlortermine are Schedule III drugs that have less abuse potential but are not very popular with practicing physicians. Adrenergics in the DEA Class IV include medications fre-

quently used on a short-term basis in the United States. These include phentermine, diethylpropion and mazindol. Phentermine and diethylpropion stimulate release of norepinephrine from nerve terminals in the central nervous system. Mazindol inhibits reuptake of norepinephrine. All three of these drugs have minimal addiction or abuse potential (41). Griffiths et al (41) demonstrated in non-human primates that diethylpropion had somewhat higher reinforcement potential than did phentermine. Silverstone (32) concluded that all of the drugs in this category produce approximately the same weight loss.

Some over-the-counter obesity drugs contain PPA which has α-catacholamine agonist action in the parventricular nucleus causing a decrease in food intake. PPA, found in appetite suppressants and in cough and cold medications, has been shown to be an independent risk factor for hemorrhagic stroke (21) and recently preparations containing PPA have been withdrawn from the market by the Food and Drug Administration (FDA) (http://www.fda.gov/cder/drug/infopage/ppa/default.htm).

Serotonergic Stimulation Sibutramine is the only currently approved obesity drug that prevents the reuptake of serotonin in the neural clefts. Fluoxetine and sertraline are specific serotonin reuptake inhibitors not approved specifically by the FDA for weight loss or appetite control but that have been demonstrated to reduce food intake in animals and have been shown to produce weight loss in humans in short-term trials. However, weight returned to pretreatment levels after 1 year (42). Recently the FDA approved the use of fluoxetine in the eating disorder bulimia nervosa (http://vm.cfsan.fda.gov/dms/fdeatdis.html).

Adrenergic and Serotonergic Stimulation The combination of fenfluramine, a serotonin agonist, and phentermine, an adrenergic agonist, was first reported in 1984 by Weintraub et al (43). Fenfluramine or dexfenfluramine in combination with phentermine (fen–phen) enjoyed short-term success in the treatment of obesity (28,29,44). The combination is no longer available as dexfenfluramine and fenfluramine have been taken off the market because of the development of

left heart valvulopathy in a significant number of patients taking these drugs (20). Other side-effects associated with the fenfluramine component of this combination included possible pulmonary hypertension, short-term memory loss, and the serotonin syndrome. Fenfluramine and its major metabolite (D-norphenfluramine) released serotonin from nerve endings and also blocked its reuptake. The combination of fen–phen was highly effective in producing weight loss and its absence from our armamentarium has left quite a vacuum.

Many practicing physicians have used fluoxetine or other selective serotonin reuptake inhibitors, which have excellent side-effect profiles, in combination with phentermine (45) in an attempt to duplicate the results of fen–phen (29).

Sibutramine was initially evaluated as an antidepressant because of its ability to inhibit the reuptake of norepinephrine and serotonin in a manner similar to other antidepressants such as venlafaxine. Sibutramine was found to be associated with weight loss and was not that effective as an antidepressant. The drug is now marketed for weight loss. It has the advantage of a combination of adrenergic- and serotonergic-like activity. Sibutramine inhibits serotonin reuptake in a manner similar to that of the selective serotonin reuptake inhibitors. Unlike fenfluramine, it does not cause release of serotonin. Sibutramine has no dopaminergic effects, and no evidence of addictive potential. Sibutramine is associated with decreased appetite and increased satiety (46). Animal studies have demonstrated increases in metabolic rate for more than 6 h after the drug was given. Side-effects associated with noradrenergic agonists include insomnia, nervousness, dry mouth, and constipation. They can also affect blood pressure, cause increased heart rate, and palpitations. A history of coronary disease, congestive heart failure and/or arrhythmias as well as stroke or transient ischemic attack would preclude the use of this medication. Serotonergic drugs are not indicated for use with other selective serotonin reuptake inhibitors which may precipitate the serotonin syndrome (47), or with monoamine oxidase inhibitors.

Peripherally Acting Agents

Orlistat is a pancreatic lipase-binding agent that reduces fat absorption in the gastrointestinal tract (48,49). The drug, recently approved by United States FDA, is essentially not absorbed systemically, and its side-effects are limited to those resulting from the inhibition of dietary fat absorption. Increased gas and flatulence, cramping, diarrhea, oily rectal discharge and soilage are common, particularly in the initial period of treatment. These side-effects improve with time and reductions of the indiscretions in the diet which may precede them. About one third of the dietary fat absorption is blocked by orlistat with concomitant caloric loss in the stool. In a diet containing 30% calories as fat, this can lead to a significant relative negative energy balance. Fat-soluble vitamin supplements are recommended with the use of orlistat with an appropriate interval between the vitamin and lipase inhibitor intake.

Experimental and/or Drugs Not Currently Approved for Obesity Treatment

Acarbose is an α-glucosidase inhibitor that reduces digestion of complex carbohydrates leading to undigested food stuffs entering the colon (50). This is associated with cramping, gas, abdominal discomfort, and diarrhea. This drug is approved for the treatment of diabetes in the United States but has not been very effective in weight loss trials.

Chitosan is a product promoted through the health food industry. This is a polymer of glucosamine extracted from mollusk shells and reportedly reduces fat absorption by binding dietary fat. Studies in animals on high-fat diets revealed chitosan prevented weight gain, fatty liver, and hyperlipidemia. Studies in humans are limited and not very impressive (51).

Ephedrine, a centrally and peripherally acting non-specific β-adrenergic stimulator, has been used alone and in combination with caffeine and/or aspirin in the treatment of obesity. Ephedrine directly stimulates β-adrenergic receptors and also stimulates the sympathetic nerve terminal

release of norepinephrine. Caffeine delays the degradation of ephedrine and inhibits the postsynaptic phosphodiesterase, thereby potentiating the effect of ephedrine. Caffeine also causes a mild increase in thermogenesis. Aspirin potentiates and prolongs the norepinephrine activity by interfering with prostaglandins, which degrade norepinephrine in the neural cleft. The non-specific nature of the β-agonist stimulation effect on β-I and -II receptors may cause an increased blood pressure and/or heart rate as well as nervousness and tremor during the initial phase of treatment. There is also an associated rise in serum insulin levels. Tachyphylaxis usually eliminates the symptoms related to the β-I and -II stimulation within 1 month, but there is evidence that the β-III stimulation continues, as the increase in metabolic rate persists. There are many studies confirming these findings (37,38,52).

There is currently concern regarding the health food industry's marketing of supplements that contain these three ingredients: Ma Huang, a Chinese herb containing ephedrine; coffee beans; and acetosalicylic acid from willow bark. Because 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 (FTC) have become concerned and issued warnings because a number of people have had cardiac events or even died while taking these compounds (53), but a direct cause and effect relationship has not been established.

Conjugated linoleic acid has been shown to increase lean body mass in animals, especially in growing young animals. Trials of this medication on weight loss have not been effective; however, there are ongoing trials to determine if a regain in weight would be more likely to be lean body mass rather than adipose tissue (54,55).

Green tea extract contains caffeine and catechin polyphenols, which have been found to increase peripheral thermogenesis. A small study in humans revealed a 3.4% increase in 24-h energy expenditure, and a 25% increase in the fat oxidation (56). Studies on weight loss have not been reported.

Hydroxycitric acid plays a part in inhibiting *de novo* lipogenesis. Hydroxycitric acid is the active ingredient of the fruit *Garcinia cambogia*. Therefore, hydroxy citrate and *Garcinia cambogia* are hypothesized to have a role in weight loss. However, a 12-week randomized double-blind placebo-controlled trial in 135 overweight men and women failed to show significant weight loss differences that could be attributed to *Garcinia cambogia* (57).

Potassium, magnesium, and phosphate in orange juice reportedly increase the thermic effect of food in overweight women (58,59). Obesity has been associated with decreased levels of skeletal muscle potassium and serum phosphate. The authors of these studies (58,59) assumed that the pool of potassium, magnesium, and phosphate is low in obesity and replenishing these minerals may increase thermogenesis. Potassium, magnesium, and phosphate electrolytes were added to orange juice. This combination facilitates the intercellular transfer of potassium with the insulin and increases the sodium/potassium adenosine triphosphatase activity, which has high energy cost. A 6.3% increase in energy expenditure was noted in 30 min in the electrolyte plus orange juice group compared to the group receiving only orange juice. Further studies of this phenomenon may be in order.

Metformin, a biguanide oral antihyperglycemic drug is known to improve insulin sensitivity as well as decrease static glucose production and decrease intestinal glucose absorption. Obesity is known to be associated with hyperinsulinemia and insulin resistance. Studies indicate that it may be useful in inhibiting food intake, lowering body weight and body fat in the non-diabetic obese patient as well as the diabetic (60–62). It has been effective in some of the metabolic abnormalities associated with polycystic ovary syndrome.

Topiramate is an antiepileptic drug which has recently become available in the United States and in many European countries and it is indicated in partial-onset seizures. It was noted that "weight loss" and "anorexia" were two of the side-effects of the drug, along with central nervous system related symptoms such as dizziness, fatigue, visual disturbances, ataxia, impaired concentration, and

nephrolithiasis (63,64). The effect of topiramate on body weight has received significant attention. Many antiepileptic drugs are known to increase body weight and the observation of topiramate-induced weight loss may have application in weight reduction of some obese patients, particularly in treating patients with mood disorders and obesity as well as some binge eaters (65,66).

Cytomel: triiodothyronine (T3) levels have been noted to decrease with rapid weight loss, starvation or restricted caloric intake. There is a concomitant increase in reverse T3 which is much less metabolically active. Attempts to treat this drop in T3 with cytomel has led to slight increases in weight loss but also to increased muscle catabolism, the additional weight loss being at the expense of lean body mass and not adipose tissue (67,68). Cytomel is not recommended at this time, but further studies may be in order. Previous history of thyroid hormone (T4) treatment for obesity was met with less than satisfactory results and significant side-effects, and is no longer considered an option.

Leptin, the hormone secreted by adipocytes, was discovered in 1994 and acts directly or indirectly through specific receptors in the central nervous system to decrease food intake and increase energy expenditure. It also influences glucose and fat metabolism and has other neuroendocrine functions. The multiple targets of leptin and its interactions in the central nervous system and periphery have opened a vast number of pathways that affect energy balance (25,69). The optimism about the role of leptin in the treatment of human obesity was dampened by the findings that most obese humans have elevated levels of leptin (70). However, a recently published clinical trial of leptin injections vs. placebo showed a significant dose–response effect for weight loss in the leptin group (71). Weight loss produced in 24 weeks in the highest dose leptin group was 7.1 kg, compared to 1.7 kg in the placebo group.

CRITERIA FOR RECEIVING OBESITY DRUGS

In 1996 the National Institutes of Health Taskforce on the Prevention and Treatment of Obesity did not recommend

long-term drug therapy for obesity until additional research had been performed (72). The FDA guidelines stipulated a BMI of $30\,kg/m^2$ ($27\,kg/m^2$ with comorbidities) or more be used as a basis for considering drug therapy (73). In 1995, the North American Association for the Study of Obesity (NAASO) convened a board including members from the FDA and National Institutes of Health (NIH) suggesting a slightly lower limit of BMI (74). However, more recently, NAASO endorsed the National Heart, Lung, and Blood Institute (NHLBI) guidelines (75), which set the BMI thresholds for treatment somewhat higher. Shape Up America! and the American Obesity Association have added their recommendations (76). According to the NHLBI guidelines, which are the most recent guidelines, individuals with a BMI of 25–29.9 are considered overweight, and individuals with a BMI ≥ 30 are considered obese. Treatment of overweight with drugs is recommended only when two or more risk factors are present. An initial goal for weight loss might be 10% weight loss below baseline and, upon reaching the goal, further weight loss may be attempted if indicated by further evaluation. The rate of weight loss should be about 0.5–1 kg/week. Greater rates of weight loss may compromise safety. The guidelines further state that weight loss and maintenance therapy should use the combination of reduced calories, increased physical activity, and behavior therapy. As an adjunct to this strategy, weight loss drugs approved by the FDA may be used for patients with a BMI ≥ 30 with no concomitant obesity-related risk factors or for patients with a BMI ≥ 27 with concomitant obesity-related risk factors. The lifestyle changes which are essential for long-term success must be a priority. Physicians must pay close attention to appropriately screening candidates suitable for drug treatment of obesity and should also be very vigilant about noting adverse effects, if any, of the pharmacotherapy. The relative and absolute contraindications to drug therapy are listed (Table 5-2).

CRITERIA FOR SUCCESSFUL WEIGHT LOSS

Weight loss is a surrogate measure used to define fat loss. Present evidence points to fat loss as the measurement

Table 5-2 Contraindications or Cautions to the Use of Obesity Drugs

1. Pregnancy or lactation
2. Unstable cardiac disease
3. Uncontrolled hypertension
4. Unstable severe systemic illness
5. Unstable psychiatric disorder or anorexia
6. Other drug therapy, if incompatible (e.g. monoamine oxidase inhibitors, migraine drugs)
7. Closed angle glaucoma (caution)
8. General anesthesia (absolute contraindication, except emergencies)

related to beneficial effects on longevity and health (77). The FDA recommends that before a drug can be considered for approval it must lead to a weight loss ≥ 5% more than that achieved by a placebo and be statistically significantly greater (73). Improvement in comorbidities, such as diabetes, hypertension, hyperlipoproteinemia, respiratory insufficiency, sleep apnea, heart failure, and arthropathies, should be documented and used to evaluate the effectiveness of the drug. It is well documented that health risk factors associated with obesity are frequently ameliorated with as little as 5–10% weight loss (78). Ten per cent weight loss is a reasonable loss to expect with comprehensive weight loss programs, and that includes drug therapy where and when indicated. The weight loss slows down after the first few weeks when most overweight patients lose some water weight. It should be noted that the amount and the rate of weight loss is usually proportional to the starting weight of the person. People committed to lifestyle change and long follow-up have experienced much greater loss and have been able to maintain it; however, these are the exceptions. Most people regain all or part of their weight because they frequently stop treating their disease. The failure to maintain weight loss is in part a result of failure to continue treatment.

Few patients treated with drugs reach their goal weight and almost nobody reaches their "ideal" weight. The focus

of the treatment should be on improving the physical and mental health of the patient and not on achieving an unrealistic dream weight (79). It is important to explain to the patients that obesity is a chronic condition and that weight management is a lifelong process.

SUGGESTIONS FOR THE USE OF OBESITY DRUGS

Recidivism is a more significant problem in obesity than in other chronic diseases. There is a strong feeling among practitioners and scientists treating and studying this disease that long-term—possible lifelong—therapy, including judicious use of drugs, may be indicated. The NHLBI, in their guidelines (75), suggest that an obesity medication may be taken indefinitely if it continues to be associated with weight loss and has no serious side-effects. This is with the understanding that treatment periods greater than 1 year have not been well studied and safety and efficacy must be continually monitored.

Recommended starting doses for more commonly used drugs are listed in Table 5-1 (46). Maximum doses are also listed. These drugs not infrequently have side-effects and lower starting doses may obviate some of them; tachyphylaxis may develop to lessen some of the other side-effects. It is recommended that obesity treatment be started with lowest possible effective dose and the adverse effects (if any) be carefully monitored. At every clinic visit, patients should be shown a list of possible serious drug-related side-effects and patients should be asked to check whether any of these apply. This practice may result in overestimating the prevalence of adverse effects; however, it might be better to exaggerate the adverse effects than to miss them. If the adverse effects are serious and life-threatening, or intolerable, the drug should be withdrawn. In cases where the adverse effects are serious but not life-threatening, dosage may be reduced under extreme vigilance, the drug may be changed, or the drug treatment may be stopped completely. Some adverse effects may decrease in intensity (or cease) over time. Weight loss progress should be considered if the adverse effects of a

drug are mild or absent. Drug dosage need not be increased if the weight loss is satisfactory (≥1 lb week). Compliance with other components of the program, such as diet and lifestyle modification, should be ascertained if the weight loss is <1 lb for at least two consecutive weeks. Drug dosage may be increased if the weight loss is slow or unsatisfactory. Increase in drug dosage should be in small increments. Additional caution and monitoring for adverse effects should be exercised whenever a drug dosage is increased. Generally, the increased drug dosage should be reduced to previous levels if no additional weight loss is obtained.

The possibility of potential adverse effects of an obesity drug warrants screening of potential responders and non-responders to the drug treatment. To minimize the risk of adverse effects, drugs could be discontinued for the potential non-responders if they could be identified early during the treatment. Various predictors of drug-induced weight loss have been suggested. The package insert for dexfenfluramine recommended re-evaluation and possible discontinuation of the drug for patients losing >1.81 kg (4 lb) in the first month of treatment based on studies carried out by the manufacturer. The cut-off of a 4-lb weight loss in the first month of treatment was used widely by physicians to determine non-responders to fen–phen combination treatment. This criterion has become the standard for evaluating the response to most antiobesity drugs (76). However, a recent analysis by Dhurandhar et al (80) of weight loss response of 975 patients to phentermine and fenfluramine treatment showed that, in the total sample, first month weight loss highly correlated with percentage reduction in body mass index after 6 months of treatment. However, about 98% of the responders to the treatment (who lost >4 lb in the first month) had a weight reduction of 5% or greater in 6 months and 76% of the non-responders (who lost <4 lb in the first month) had met or exceeded the NAASO criteria for the success of a drug treatment (≥5% weight loss). Even the adverse effects after 6 months of treatment and the dropout rates after 1 year of treatment were not significantly different for non-responders vs. responders. This study indicated that although the first month weight loss predicted the long-

term response to fen–phen treatment, it was inadequate in identifying the non-responders and may unnecessarily preclude potential beneficiaries of the treatment. A good criterion to identify non-responders early in the drug treatment remains to be defined.

RESULTS OF DRUG TREATMENT OF OBESITY

Single Drug Trials

Criteria for patient selection, as well as approaches and skills of physicians conducting studies and treatment programs associated with drug therapy are quite variable and make evaluation of results difficult to interpret. Most clinical trials have used single drug therapy. A review of over 200 studies by Scoville in 1976 revealed that the drugs available at that time were associated with approximately 0.5 lb/week greater weight loss than with placebo (81). Silverstone (32) reached similar conclusions when comparing short-term results from different agents.

Long-term studies that have evaluated obesity drugs for longer than 1 year are limited in number. Goldstein and Potvin (82) found only nine studies that had followed subjects for 1 year or more (Table 5-3). As seen in Table 5-3, 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 placebo. Even the placebo weight losses in several studies were very good, demonstrating that both groups underwent standard obesity therapy with diet, exercise, and behavioral therapy, which contributed to the weight loss observed. For example, mazindol produced the largest weight losses (14.2 kg) seen with a single agent in the review (82) but the large weight loss in the placebo group (10.2 kg) suggests that the behavioral component was very effective in this study.

Fluoxetine produced good weight loss over the first 6 months of treatment, although weight regain occurs thereafter and 1 year weight was not different between the placebo and experimental groups in 8 of 10 studies reported in a summary paper by Goldstein et al (83). Two sites that

Table 5-3 Long-Term Clinical Trials with Antiobesity Drugs

Antiobesity Drug	1 Year Weight Loss (kg)	
	Placebo	Active Agent
Diethylpropion	−10.5	−8.9
Mazindol	−10.2	−14.2
	−	−12.0
Fenfluramine	−4.5	−8.7
Dexfenfluramine	−7.2	−9.8
	−2.7	−5.7
	−4.6	−5.2
Fluoxetine	+0.6	−13.9
	−4.5	−8.2
	−1.5	−2.3
Sibutramine	−1.8	−6.0
Orlistat	−5.8	−8.8

included strong behavioral programs were able to obtain significant weight loss at 1 year (42,84).

Sibutramine, the latest centrally acting obesity drug approved by the FDA, produced weight losses of about 7–10 kg in a dose-dependent manner (85,86). Weight loss is very rapid in the first 12 weeks of treatment but does continue through 24 weeks of treatment. Treatment with sibutramine has been shown to reduce many of the risk factors associated with obesity such as cholesterol, triglycerides, and low-density lipoproteins (LDL), but reduction in blood pressure was noted to be less than with placebo with similar weight loss. Blood pressure and heart rate may actually increase in some patients and must be monitored closely, especially early in therapy. Patients should be very carefully followed-up and the medications should be stopped if weight loss is not satisfactory or if blood pressure rises.

Orlistat produces about 10% loss of initial body weight compared to about 6% weight loss in the placebo group (87). First year weight loss for the orlistat-treated group in a double-blind placebo-controlled trial (88) was 8.76 kg compared to 5.81 kg in the placebo group ($P < 0.001$). Subjects

of this trial continuing to receive the drug for 2 years had significantly less weight regain in the second year compared to the placebo group. The orlistat group had improvement in fasting LDL-cholesterol and insulin levels. In another trial, 729 obese patients losing >8% of their body weight on hypocaloric diet were treated with orlistat (30, 60, or 120 mg three times a day), or placebo, for 1 year (48). After 1 year, the subjects treated with 120 mg orlistat regained significantly less weight than the placebo group (32.8 vs. 58.7%, $P < 0.001$). Another study reported that orlistat treatment for 2 years promoted weight loss and minimized weight regain, improved lipid profile, blood pressure, and quality of life (49).

Combination Treatment

The combination of fenfluramine, a serotonin agonist, and phentermine, an adrenergic agonist, was first reported in 1984 by Weintraub et al (43). Weintraub et al (29) next performed a 4-year follow-up study that generated an enormous amount of publicity and changed the perception of the use of drugs for obesity. Although the combination of phentermine with fenfluramine or dexfenfluramine had a sudden demise when valvulopathy was reported in 1998, the combination was a highly effective drug regimen for weight loss. The fen–phen regimen popularized the concept of using more than one drug for treating obesity. The regimen also demonstrated that two drugs could be used in smaller than usual doses, minimizing adverse effects while enhancing the weight loss effect of the drugs.

The use of fluoxetine (20–60 mg/day) in combination with phentermine (18.75–37.5 mg/day) for 6-month periods produced significant weight loss (45). Whether longer periods of use of this combination will alleviate the regain noted with fluoxetine alone has not been studied to date.

Drug combinations such as ephedrine, caffeine, with or without aspirin, have produced weight losses that are as good as any drugs reported to date. Toubro et al (36) 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 taken. This combination opened the door for further studies of combination drug therapy or stepwise therapy as an option for treating obesity. It is to be hoped that combination drug therapy with less significant or more tolerable side-effects will be developed in the future.

A COMPREHENSIVE WEIGHT MANAGEMENT PROGRAM

Obesity drugs should be only one part of a comprehensive program that includes dietary alterations, and increased physical activity; that is, alteration of behavior to attain a healthier lifestyle. A detailed description of the guidelines to set up an outpatient drug treatment program are published by Dhurandhar et al (89–91). These guidelines include special considerations for the patients, staff recruitment, clinic layout, and for the treatment itself. This article also deals with various related issues, such as dealing with the adverse reactions of obesity drugs, insurance issues, frequency of visits, and group therapy vs. single patient format.

Because obesity is a chronic condition, education of patients is critical. Physicians may not have the time needed to educate the patients extensively. Several guidelines suggest that obesity drug 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 (74,76). Successful treatment of obesity will require increased awareness among patients and physicians, as well as the third party payees, that obesity is a chronic disease.

Reasonable and realistic weight loss goals in the range of 10% of the starting weight must be emphasized. At the same time, patients should be encouraged by the fact that weight loss can vary tremendously, and their response and the rate of weight loss is hard to predict accurately. Maintenance of the weight lost is the most important component of a weight management program. During their lifetime,

many obese individuals lose (and regain) hundreds of pounds of weight. Health care professionals as well as patients should realize that successful weight loss is only the beginning of the battle. Preventing weight regain is truly the difficult aspect of weight management. Obesity drugs are currently used for producing weight loss. It is hoped that future research discovers drugs that could be used in the long term to prevent weight regain.

CONCLUSIONS

Obesity requires lifelong treatment. Drug therapy is in its infancy and long-term use of many of the drugs has not been adequately evaluated to date regarding either safety or efficacy. Weight loss with present medications is limited and usually plateaus in 6 months and after about 10% weight loss. There is evidence that patients may maintain the weight loss when the pharmacotherapy is continued in conjunction with a comprehensive weight management program. Weight management programs include physicians, dietitians, nurses, exercise physiologists, psychologists, and/or counselors.

Like any other drug, obesity drugs have a potential for adverse effects and minimizing the risk of such adverse effects should be a major concern. Drug therapy should be reserved for those patients with medically significant obesity with a favorable benefit:risk ratio. Candidates for drug treatment should be carefully screened. Careful follow-up and continuous assessment for efficacy and appearance of side-effects is mandatory.

A well-grounded weight management program including appropriate use of drugs and surgical referral capability allows the obese patient the best opportunity to obtain and retain a significant healthy weight loss.

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