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## Obesity Part 2: Pharmacotherapy

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### Abstract

Like hypertension or diabetes mellitus, obesity is a chronic disease that requires continued treatment. Short-term (weeks or months) treatment with drugs is not warranted nor is it probably appropriate. Treatment with medication is likely to be necessary for years, and perhaps for a lifetime in order to sustain weight loss and improve health. To date, there have been few published studies where patients have received anorexiant for more than 1 year. In addition, data on the long-term safety and efficacy of anorectic drug combinations is also very limited. The lack of long-term safety and efficacy data is disappointing, given that most of these anorexiants have been available for more than 20 years. Accordingly, the National Task Force on the Prevention and Treatment of Obesity does not recommend pharmacotherapy for the routine treatment of obesity.<sup>56</sup> Despite this recommendation, there has been a resurgence in the prescribing of diet pills.

Although routine use is not justified, some carefully selected patients may benefit from pharmacotherapy. Most authorities recommend a BMI of 27 as the minimum indication for drug therapy in the absence of obesity-related comorbidities who have failed diet, exercise, and behavior modification.<sup>56</sup> Labeling information for dexfenfluramine is more conservative and recommends a minimum BMI of 30 Kg/m<sup>2</sup> for treatment, or BMI 27 kg/m<sup>2</sup> when other obesity-related risk factors are present.<sup>57</sup> If drug therapy is warranted, it should only be used in conjunction with a comprehensive program that includes nutrition education, exercise if appropriate, and behavior modification. In addition, therapy should only be continued if the patient has an initial response.<sup>56</sup>

The average weight loss is modest compared to that

attributed to placebo. Net weight loss attributable to drug therapy typically ranges from 2 to 10 kg.<sup>56</sup> Response is variable with some patients losing little or no weight, and others responding with large and clinically important weight loss. Unfortunately, it is not yet possible to predict who will respond to pharmacotherapy. There is some evidence that clinically significant weight loss within the first several weeks of treatment with a given drug is predictive of further responsiveness to the same drug. Thus, an initial trial period of several weeks with a drug or drug combination may help determine their efficacy. If the patient fails to respond to a given drug or combination of drugs with a reasonable degree of weight loss such as 0.45 kg per week after a 4-week trial period, therapy should be reassessed. Reassessment should include an evaluation of compliance to the drug regimen, as well as any adjunctive therapies, and assessment of the need for a dosage adjustment. If the patient continues to be unresponsive, the medication should be discontinued. Ongoing monitoring is essential and should include assessment for adverse effects.

A wide variety of pharmacologic substances have been used for the treatment of obesity and are reviewed in the discussion that follows. Current pharmacotherapy for obesity includes drugs that decrease caloric intake by suppressing appetite and thermogenic drugs that increase metabolism. Future approaches are likely to involve drugs that block gastrointestinal absorption of nutrients, as well as more specific agents that alter the neurochemical or hormonal signals that affect fat stores, food intake, and energy expenditure.

Eventually, obesity may also lend itself to novel therapeutic approaches involving gene therapy. Although there is a consensus that obesity is associated with significant morbidity and mortality and that modest degrees of weight loss may result in health benefits for some obese persons, <sup>1,42</sup> it must be emphasized that it is not yet known whether or not drug-induced weight loss leads ultimately to lower morbidity and mortality. Studies evaluating the effect of drugs for the treatment of obesity invariably use weight as the chief endpoint and have not included major morbidity endpoints or mortality. Without this information, the risk-benefit ratio cannot be established.

### HISTORY

The fascinating and sometimes disturbing history of drug therapy for obesity dates back to 1893 with the introduction of thyroid hormone. <sup>58</sup> Thyroid extract was believed to be therapeutic because obese persons were thought to have a low metabolic rate. Amazingly, doses of up to 25 grains (equivalent to 1,500 mg of desiccated thyroid or about 75 mg of synthetic levothyroxine!) were used. This treatment was in vogue well into the 1970s but was abandoned because of the risk for electrolyte disturbances, metabolic imbalances, and cardiac dysrhythmias. Excessive thyroid hormone supplementation increases bone resorption leading to decreased bone density and osteoporosis. In addition, the hormone may have a detrimental effect on lean body mass. On May 15, 1978 the FDA issued a final ruling warning against the use of thyroid preparations for the treatment of obesity. Thyroid hormone preparations are therefore not indicated for the treatment of obesity unless the obese patient is hypothyroid.

Dinitrophenol (2,4-DNP) was introduced in 1933 for the treatment of obesity and soon found its way into numerous “anti-fat” patent medicines. <sup>59</sup> Dinitrophenols induce weight loss by uncoupling oxidative phosphorylation, thereby markedly increasing the metabolic rate and body temperature. <sup>58</sup> However, the use of these compounds was abandoned in 1937 because of reports of severe intoxications and deaths. Dinitrophenol is used currently as a wood preservative and insecticide.

The use of cardiac glycosides, alone or as an ingredient in bizarre weight loss concoctions, was popular during the first half of this century. Digitalis, pushed to the point of toxicity to induce nausea and therefore anorexia, was advocated in

1940<sup>60</sup> and was in vogue until the late 1960s when reports of cardiac dysrhythmias surfaced. <sup>61</sup> Digitalis was typically added to weight control regimens for its anorexic action and to counteract the tachycardia produced by the supraphysiologic doses of thyroid hormone. The cardiac glycoside strophanthin was actually combined with thyroxine in a commercial product known by the brand name of Neo-Barine which was advertised as a “safe, dependable anti-adipoexic weight-reducing agent”. <sup>62</sup> Neo-Barine was commonly used for weight reduction but was cardiotoxic prompting the June 19, 1964 Medical Letter on Drugs and Therapeutics to brand it as a dangerous drug and recommend its removal from the market. <sup>62</sup>

A 1969 report in the Journal of the American Medical Association highlighted the problems with polypharmacy in the treatment of obesity. The report describes a 19 year old male who died from a weight reduction program that included the combination of thyroid extract, digitalis, amphetamines, and diuretics. <sup>63</sup> Prior to his demise from hypokalemia and cardiac dysrhythmia, the patient was taking 0.65 grams of thyroid (roughly 0.55 mg of levothyroxine), 50 milligrams of digitalis (roughly 0.125 mg of digoxin), 25 mg of amphetamine, 500 mg of potassium gluconate, and 50 mg of chlorthalidone (a thiazide diuretic).

In the 1970s, ephedrine-containing products used in Europe for the treatment of asthma were noted to cause anorexia and weight loss in asthmatic patients. In 1972, a Danish physician by the name of Dr. Eriksen in Elsinore observed loss of appetite and weight in asthmatic patients for whom he had prescribed a mixture containing ephedrine, caffeine, and phenobarbital. Rumor spread and when sales culminated in 1977, more than 70,000 Danes were taking what became known as the “Elsinore pill”. One provincial pharmacy alone was manufacturing a million tablets weekly. <sup>64</sup> Another asthma product containing ephedrine known as the Do-Do pill, which was available over the counter in England, was studied. <sup>65</sup> These observations prompted further research that revealed how methylxanthines (caffeine and theophylline) potentiate the thermogenic effect of ephedrine - which stimulated interest in the combination. <sup>66</sup>

Dextroamphetamine was observed to cause weight loss after it was introduced in the 1930s for the treatment of narcolepsy. <sup>58</sup> The amphetamines were subsequently shown to induce weight loss by suppressing appetite but enthusiasm faded as the potential for abuse became apparent. Problems

with amphetamine abuse dampened enthusiasm for drug therapy resulting in a 23 year hiatus from 1973 when the FDA approved fenfluramine to 1996 when dexfenfluramine was approved. The introduction of the fenfluramines, drugs that resemble the amphetamines chemically but not pharmacologically, vastly increased the understanding of the role of serotonin (5-hydroxytryptamine) in food intake and ushered in the current era of pharmacotherapy of obesity.

### **NORADRENERGIC AGENTS**

The extreme central nervous system excitation caused by the amphetamines led to the development of noradrenergic derivatives possessing anorexiants activity with less potential for abuse. Noradrenergic, or norepinephrine-like, agents promote weight loss by suppressing appetite and may also increase energy expenditure. They act by promoting the release of norepinephrine and dopamine from nerve terminals in the central nervous system and by blocking the subsequent reuptake.<sup>67</sup>

Phenteramine, phendimetrazine, phenmetrazine, diethylpropion, benzphetamine, and mazindol are the prescription noradrenergics currently available in the U.S.. Phenylpropanolamine is widely available over-the-counter without a prescription.

Phenteramine (Fastin, Ionamin, and others) is probably the most commonly prescribed noradrenergic and is commonly prescribed with the serotonergic agent fenfluramine (Pondimin). Phenteramine provides the noradrenergic activity when combined with fenfluramine in the combination popularly referred to as “Fen-Phen”. Amphetamines are rarely prescribed for the treatment of obesity because of the potential for abuse and because safer alternatives are widely available. In fact, the prescribing of amphetamines for the treatment of obesity is severely restricted by medical and pharmacy laws in many states.<sup>56</sup>

In most randomized controlled studies, ranging from 6 to 64 weeks in duration, the noradrenergic anorexiants promoted significantly greater weight loss than placebo. The rate of weight loss attributed to these drugs averages 0.32 kg (0.7 lbs) per week. Weight loss continues as long as the drugs are taken but tends to be regained when treatment stops.<sup>58</sup>

Although the effectiveness of over-the-counter phenylpropanolamine has been questioned, a randomized, double-blind, placebo-controlled study revealed a modest short-term benefit. One-hundred and one overweight subjects randomized to phenylpropanolamine (75 mg of a sustained release product daily) had lost an average of 2.6 kg at 8 weeks compared to only 1.1 kg for those who received placebo. The weight loss persisted in the 36 patients who chose to remain in the study for an additional 12 weeks. No difference in blood pressure or side effects were observed.<sup>68</sup>

All of the noradrenergic agents are contraindicated in patients taking monamine oxidase inhibitors (MAOI) because of the danger of hypertensive crisis. Common side effects associated with this class of drugs include heart palpitations, tachycardia, nervousness, restlessness, insomnia, anxiety, tremors, and dry mouth. Most of the noradrenergic agents cross react with some urine amphetamine assays. Therefore, patients should be informed that urine drug screens for amphetamines may be falsely positive for up to 24 hours or more following a dose. A comprehensive drug information compendium or manufacturer prescribing information should be consulted for complete prescribing and patient information.

### **SEROTONINERGIC AGENTS**

**FENFLURAMINE AND DEXFENFLURAMINE:** The two most commonly prescribed serotonergic anorexiants are fenfluramine (Pondimin) and dexfenfluramine (Redux). Antidepressants, such as Prozac, that selectively inhibit the reuptake of serotonin have also been studied and are discussed later. Fenfluramine and dexfenfluramine induce the release and inhibit the reuptake of serotonin (5-hydroxytryptamine, 5-HT) in the brain.<sup>69, 70</sup> Elevated brain serotonin levels are associated with early satiety and appetite suppression.<sup>67</sup> Although weight loss from serotonergic agents has traditionally been ascribed to their anorectic effects, there is evidence suggesting that these drugs are also capable of increasing energy expenditure.<sup>71, 72</sup> Fenfluramine is a racemate of the dextro- and levo-rotatory isomers of fenfluramine and is commonly used with phenteramine in the “Fen-Phen” combination. Dexfenfluramine is simply the biologically active dextro-rotatory stereoisomer of fenfluramine which has been available in Europe for many years and was recently approved by the FDA in the United States.<sup>73</sup>

Although there have been several well-controlled studies of single-drug therapy,<sup>74 75 76 77</sup> only one long-term controlled study of combination therapy has been published.<sup>78 79 80 81 82 83 84 85 86</sup> In studies conducted for 6 months or longer, both single-drug and combination therapy induced a net weight loss ranging from 2 to 10 kg.

The rationale for the aforementioned combination of fenfluramine and phenteramine is that, by combining drugs with different mechanisms of action, a lower dose of each drug can be used thereby maintaining efficacy and minimizing toxicity. In 1984, Weintraub and coworkers showed that the combination of low doses of fenfluramine and phenteramine resulted in weight loss equal to that achieved with either agent alone.<sup>87</sup> Patients who took the combination reported significantly fewer cardiovascular and central nervous system side effects than patients who took phenteramine alone. Subsequently, in 1992 Weintraub and colleagues published the results of a multi-phase study using the combination of fenfluramine and phenteramine.<sup>78-86</sup> Because this landmark series of studies is widely cited as justification for the routine use of “Fen-Phen” and is partly responsible for the recent resurgence in the use of diet pills for weight loss, the design and results are outlined in some detail.

One-hundred and twenty one obese persons were provided with 6 weeks of intensive behavior modification and individualized dietary and exercise instruction. Following this initial phase, the subjects were randomly assigned to receive either a combination of fenfluramine (60 mg daily) and phenteramine (15 mg daily) or placebo. The behavior modification, exercise, and dietary instruction were provided to all of the subjects throughout the entire study period. During the initial double-blind phase of the study, that lasted 28 weeks, those taking fenfluramine-phenteramine lost significantly more weight than those taking placebo (14.3 kg versus 4.6 kg). Weight loss reached a plateau at about 18 weeks into the study but was sustained for the remaining 10 weeks of this phase of the study. After the initial 34-week phase, all subjects who remained in the study were treated with fenfluramine and phenteramine either on a continuous or intermittent basis from weeks 34 to 104. During this phase, a gradual regain of weight was observed (about 3 kg between weeks 60 and 104) in the subjects undergoing continuous therapy. In

addition, 7 of the subjects who did not respond to treatment with active drug were treated with a higher dose during this phase but still failed to respond. During the next phase of the study (weeks 104 to 156) attempts were made to optimize response using an algorithm that was designed to achieve 120% of ideal body weight while keeping side effects to a minimum. At week 156, the 51 (42%) subjects who were still participating in the study, entered into a second double-blind phase and were randomly assigned to active drug or placebo until week 190. Weight regain (4 kg between week 165 and 190) was also observed during this phase in those who received active drug. However, weight regain was less in subjects receiving active drug compared to those taking placebo. By week 190, the 27 patients still taking fenfluramine and phenteramine had lost 7 kg from baseline compared to only 2 kg for those taking placebo. At this juncture, all subjects stopped taking medication and were monitored for an additional 20 weeks during which an average of 2.7 kg of weight was regained. The bottom line is that combined treatment with fenfluramine and phenteramine produced a modest degree of weight loss above and beyond that resulting from behavior modification alone, and some effects were sustained for more than 3 years in the few patients who continued to receive active drug. Weight loss tended to reach a plateau after about 6 months, and some weight regain occurred between years 2 and 3 despite continued treatment. As observed in other studies, weight begins returning to baseline when drug therapy is stopped.

In the only published long-term (1-year), double-blind, placebo-controlled study of fenfluramine alone, weight loss was maintained in only 10 of the 42 subjects originally enrolled.<sup>74</sup> In the largest study of appetite suppressants to date, 822 obese persons on a calorie-restricted diet taking 15 mg of dexfenfluramine twice daily lost an average of 9.8 kg at six months compared to an average loss of 7.2 kg for the subjects taking placebo.<sup>75</sup> The weight loss reached a maximum at about 6 months and was sustained better with dexfenfluramine. However, 2 months after stopping treatment, both body weight and caloric intake increased to a greater extent in the patients who had been receiving dexfenfluramine, and the difference in weight loss between the dexfenfluramine and placebo group disappeared.<sup>88</sup> A

similar pattern of initial weight loss during treatment followed by weight regain after discontinuation has been observed in other studies of dexfenfluramine.<sup>89 90</sup>

Fenfluramine is indicated in the management of exogenous obesity as a short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction.<sup>91</sup> Despite the series of studies on the use of fenfluramine with phenteramine, the combination is not currently FDA approved for weight control. Dexfenfluramine is indicated for the management of obesity including weight loss and maintenance of weight loss in patients on a reduced calorie diet. The manufacturer recommends the product for obese patients with an initial body mass index (BMI) > 30 Kg/m<sup>2</sup> or BMI > 27 kg/m<sup>2</sup> when other risk factors (e.g. hypertension, diabetes, hyperlipidemia) are present. As noted by the manufacturer, the safety and effectiveness of dexfenfluramine beyond 1 year have not been established. Treatment should only be continued if the patient has an initial response which amounts to a loss of at least 1.8 kg (4 lbs) in the first month of therapy.<sup>57</sup>

All of the serotonergic agents are contraindicated in patients taking monoamine oxidase inhibitors (MAOI). Concomitant use may result in a constellation of signs and symptoms referred to as the serotonin syndrome which can be life threatening and requires immediate medical attention.<sup>57,91 92</sup>  
<sup>93</sup> The serotonin syndrome is characterized by one or more of the following signs: excitement, hypomania, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, motor weakness, myoclonus, tremor, hemiblastus, hyperreflexia, ataxia, dysarthria, incoordination, hyperthermia, shivering, mydriasis, diaphoresis, emesis, and tachycardia. A washout period of at least two weeks should elapse between stopping a MAOI and starting fenfluramine or dexfenfluramine. Patients should be off fenfluramine or dexfenfluramine for at least three weeks before the initiation of therapy with a MAOI. The use of either of these anorexiants drugs with other serotonergic agents such as the selective serotonin reuptake inhibitor class of antidepressants (e.g. fluoxetine, sertraline, paroxetine, etc.), sumatriptan (Imitrex), dihydroergotamine (D.H.E.45) may also result in the serotonin syndrome and is not recommended. Dexfenfluramine may add to the sedative effects of CNS depressants such as ethanol, benzodiazepines, and opiates.

The manufacturer of fenfluramine warns that the drug is contraindicated in patients undergoing general anesthesia because of a possible interaction with halogenated

anesthetics. Because the half-life is 20 hours, the drug should be discontinued at least 5 days prior to the administration of anesthesia to allow the body to completely clear the drug.<sup>91</sup> Unlike fenfluramine however, dexfenfluramine is not contraindicated in patients undergoing anesthesia. However, since it is chemically similar it should probably also be discontinued prior to anesthesia if possible. Dexfenfluramine is hepatically metabolized to the active metabolite d-norfenfluramine. The elimination half-life of dexfenfluramine and d-norfenfluramine is 20 and 32 hours respectively.<sup>57</sup> Therefore, dexfenfluramine should be discontinued at least 7 days prior to anesthesia.<sup>94</sup>

Adverse effects associated with dexfenfluramine include tiredness, drowsiness, diarrhea, polyuria, and dry mouth. Dry mouth is also a common complaint of patients taking the combination of fenfluramine and phenteramine. The abuse of fenfluramine or dexfenfluramine appears to be rare, although some cases have been reported with fenfluramine.<sup>95</sup>  
<sup>96</sup> Therefore these agents should probably be used with caution in patients with a history of substance abuse. Both fenfluramine and dexfenfluramine are associated with a discontinuation phenomenon, therefore it may be best to gradually taper the patient off these agents over several days when discontinuing therapy.<sup>97 98 99 100</sup> As with the noradrenergic anorexiants, patients taking fenfluramine or dexfenfluramine should be informed that urine drug screens for amphetamines may be falsely positive for up to 24 hours or more following a dose.

Appetite suppressant drugs have been implicated in the development of pulmonary hypertension since the 1960s, during an outbreak of pulmonary hypertension in Western Europe related to the use of aminorex fumarate (Menocil).<sup>101</sup>  
<sup>102</sup> Pulmonary hypertension is a often fatal disease characterized by increased pulmonary artery pressure and pulmonary vascular resistance. The predominant symptom of pulmonary hypertension is dyspnea, which can have an insidious onset. Treatment includes limiting physical stress, vasodilator drugs, and, in severe cases, heart- lung or lung transplantation.<sup>103</sup> Both fenfluramine and dexfenfluramine have been implicated in case reports and epidemiologic studies.<sup>104 105 106 107 108</sup> High doses of fenfluramine have induced acute fatal pulmonary hypertension in rats.<sup>109</sup> Dexfenfluramine has also been implicated in several case reports of pulmonary hypertension.<sup>110 111</sup> Recent epidemiologic evidence has demonstrated a statistically greater incidence of anorexiant usage (mostly with

fenfluramine and dexfenfluramine) in patients with pulmonary hypertension compared with case controls.<sup>112</sup> Furthermore, longer periods of anorexiants usage were associated with an increasing relative risk of pulmonary hypertension. Although the risk does appear to be small (28 cases per million person-years of exposure) it is nevertheless an important risk because pulmonary hypertension can be fatal.

Certain environmental factors may unveil the presence of pulmonary hypertension related to anorexiant. Ascent to moderate altitude induced high-altitude pulmonary edema (HAPE) on two separate occasions in a 41-year skier with asymptomatic pulmonary hypertension who had taken fenfluramine and diethylpropion.<sup>113</sup> HAPE is an uncommon but dangerous complication of acute mountain sickness that rarely occurs at moderate altitudes below 2,500 meters.<sup>114</sup> Thus, this case report suggests that asymptomatic pulmonary hypertension related to anorexiant may declare itself in the form of HAPE upon ascent to altitude. Patients taking anorexiant, who plan to ascend to altitude, should be advised to report any symptoms suggestive of HAPE or pulmonary hypertension such as dyspnea, exertion, cough, orthopnea, or cyanosis.

The risk of pulmonary hypertension is significant enough to worry some lung specialists who care for patients with the condition. A recent commentary criticized the approval of dexfenfluramine and warned of another epidemic of anorexiants-induced pulmonary hypertension.<sup>115</sup> The mechanism involved in the development of pulmonary hypertension is not entirely clear but recent evidence strongly suggests a role for serotonin.<sup>116</sup> Patients must be informed of the potential for pulmonary hypertension and should be instructed to report any symptoms suggestive of pulmonary hypertension including shortness of breath or trouble breathing, swelling, chest pain, or fainting. It is essential that health professionals report any documented or suspected case of pulmonary hypertension developing in patients who are taking or who have a history of taking anorexiant to the FDA.

The submission of the new drug application for dexfenfluramine in 1994 incited debate about neurotoxicity and fenfluramines and delayed the FDA approval of dexfenfluramine.<sup>117</sup> The concern over the potential of dexfenfluramine to cause neurotoxicity stems from its ability to deplete serotonin in the brains of experimental animals. The National Task Force on the Prevention and Treatment of

Obesity, recently stated that “evidence of neurotoxic effects in humans has not been reported with fenfluramine or dexfenfluramine”, but went on to recommend further studies “evaluating the possibility of subtle neuropsychological changes, particularly with prolonged administration”.<sup>56</sup>

The recommended dosage of dexfenfluramine is 15 mg twice daily with meals. Patients should be cautioned to avoid beverages containing alcohol (since alcohol may exacerbate drowsiness) and warned to report any symptoms of pulmonary hypertension dyspnea, edema, angina, or syncope.<sup>57</sup> The recommended dose of fenfluramine is 30 mg twice daily.<sup>91</sup> The dosage of fenfluramine when used in combination with phenteramine was 15 mg daily, however the use of fenfluramine as part of combination therapy has not been FDA approved.

**SELECTIVE SEROTONIN REUPTAKE INHIBITORS:** Fluoxetine (Prozac) inhibits the reuptake and increases the availability of serotonin in the central nervous system. The mechanism by which the drug induces weight loss is not known, but serotonin is likely involved in the regulation of satiety.<sup>118</sup> During studies evaluating the antidepressant efficacy of fluoxetine, it was noted that patients tended to lose small amounts of weight. Based on this observation, some of the largest and best-designed studies of drug therapy for the treatment of obesity were conducted.

In a randomized study that included 655 obese persons, Levine and colleagues compared four different daily doses of fluoxetine with placebo and showed a dose-related effect on weight loss.<sup>119</sup> Patients who took 60 mg daily lost an average of 3.9 kg (8.6 lbs), compared to 2.16 kg (4.8 lbs) with 40 mg daily, 1.93 kg with 20 mg, and 0.54 with placebo. A one-year, multicenter, double-blind study in which 458 obese outpatients were randomly assigned to either 60 mg of fluoxetine or placebo and found that after 20 weeks, patients taking fluoxetine had lost an average of 5.1 kg (11.2 lbs), compared to 2.4 kg (5.3 lbs) lost by those taking inactive placebo. After 20 weeks, however, even though fluoxetine was continued, the average weight in both groups began to increase, and by the end of the year there was no difference in the average degree of weight loss between subjects who took fluoxetine and those of took placebo. Interestingly, the greatest treatment effect with fluoxetine was observed in the centers that provided behavioral or nutritional counseling.<sup>77</sup> A similar pattern of initial weight loss followed by weight regain despite

continued treatment has been reported in other studies.<sup>76,120</sup> In obese type 2 diabetics, treatment with fluoxetine was associated with initial weight loss and a reduction in insulin requirements during the period of weight loss.<sup>121, 122</sup>

Side effects associated with high-dose fluoxetine therapy include asthenia (weakness), somnolence, insomnia, nausea, diarrhea, sweating, nervousness, tremor, dyspepsia, sexual dysfunction, particularly delayed or absent orgasm. Some patients treated with fluoxetine for depression have had an increase in appetite and some have gained weight. Fluoxetine is not FDA approved for the treatment of obesity. Fluoxetine can help some patients lose weight for 5 or 6 months, but its continued effectiveness remains to be established, troublesome side effects can occur, and it is very expensive at the doses required.<sup>118</sup>

### THERMOGENIC AGENTS

**EPHEDRINE AND EPHEDRINE-CAFFEINE:** Ephedrine, the active constituent of various Ephedra plant species, is an alkaloid that was originally isolated by the Japanese chemist N. Nagai in 1887. Ephedrine has long been used as a nasal decongestant, central nervous system stimulant, and as a treatment for asthma.<sup>123</sup> Interest in the anorectic properties stemmed from the observation in the 1970s that asthmatics tended to lose their appetite and weight when treated with ephedrine-containing products.<sup>64</sup>

The way in which the combination of ephedrine and caffeine induce weight loss is not completely understood. Because of its noradrenergic properties, ephedrine is considered to suppress food intake via noradrenergic pathways in the hypothalamus and related areas. Ephedrine also appears to possess a thermogenic effect and therefore increases energy expenditure. The addition of a methylxanthine, such as caffeine, appears to potentiate both the anorectic and thermogenic effects of ephedrine.<sup>124</sup> The degree of weight loss attributed to the combination of ephedrine and caffeine is moderate and, when used as an adjunct to caloric restriction, has been reported to average 3.4 kg over 6 months.<sup>125</sup> Although the degree of weight loss attributable to ephedrine and caffeine has been reported to be similar to that induced by dexfenfluramine, side effects are more common with the ephedrine/caffeine combination.<sup>126</sup> Unfortunately, the combination of ephedrine and caffeine increases both systolic and diastolic blood pressure. It may also increase heart rate and may cause palpitations as well as nervousness,

headache, insomnia, and dizziness. Its use in persons suffering from heart conditions, hypertension, and diabetes is therefore not recommended.

Dietary supplements containing ephedrine and associated alkaloids (pseudoephedrine, norephedrine, N-methyl ephedrine) have been implicated in numerous adverse events and appear to pose a significant health risk. Because many of these products are advertised as “natural” or promoted as food supplements, consumers may assume incorrectly that they are safe and devoid of side effects. Some of these products appear to have been purposely misbranded and even adulterated and contain inappropriately high dosages of ephedrine.<sup>127</sup> As pointed out by the CDC, adverse effects from ephedrine may be variable and are not always dose-related. Serious adverse effects from ephedrine, such as acute cardiovascular and central nervous system stimulation, can occur even with low doses. Side effects associated with ephedrine include palpitations, tachycardia, hypertension, coronary artery vasospasm, psychosis, convulsions, respiratory depression, coma, and death. Furthermore, the combination of ephedrine with caffeine or phenylpropanolamine has also been associated with hemorrhagic stroke, seizures, mania, and psychosis. In fact, concern about the misuse and abuse of ephedrine as a diet aid and a stimulant, combined with concern about its use in the illegal synthesis of methamphetamine, has prompted the FDA to consider removing ephedrine from the over-the-counter (OTC) market.

**BETA-ADRENOCEPTOR AGONISTS (BRL 26830A):** Beta3-adrenergic receptors, which are found in brown adipose tissue, appear to be involved in promoting lipolysis and heat generation in fat. Activation of these receptors increases lipolysis and thermogenesis and thereby increases energy expenditure.<sup>28</sup> Several experimental compounds with beta-3-stimulating properties have been shown to possess thermogenic activity in humans and to induce weight loss when given with a caloric restricted diet.<sup>124</sup> One such compound, BRL 26830A, has been shown to stimulate thermogenesis in the brown adipose tissue and skeletal muscle of rats and increases the resting metabolic rate in normal human volunteers.<sup>128</sup> Two clinical studies reported improved weight loss compared to placebo when used in conjunction with caloric restriction.<sup>129, 130</sup> Another study failed to detect any difference with the use of BRL 26830A, but this was attributed to poor dietary compliance and the refractory nature of the patient population.<sup>131</sup> Tachycardia, tremor, shaky hands have been the only

routinely reported side effects which suggests some activity at beta-2 receptors.<sup>124,128</sup> None of the aforementioned thermogenic agents are currently approved by the FDA for weight control.

### LIPASE INHIBITORS

ORLISTAT: Caloric intake can also be modulated by decreasing the absorption of nutrients in the gastrointestinal tract. Orlistat (to be marketed under the name Xenical by Hoffman-La Roche), a synthetic derivative of lipostatin which is the natural product of *Streptomyces toxytricini*, is an inhibitor of intestinal lipases.<sup>132</sup> Lipase is an enzyme that breaks down fat so that it can be absorbed in the gastrointestinal tract. Inhibition of lipase causes some of the fat that is eaten to pass undigested through the body. Fifty milligrams of orlistat three times daily produced significantly greater weight loss (4.3 3.4 kg) than placebo (2.1 2.8 kg) at 12 weeks in a preliminary study involving 39 healthy obese persons. Treatment with orlistat was associated with more gastrointestinal side effects including abdominal pain, fecal incontinence, liquid or oily stools, nausea and vomiting. Orlistat also decreased blood levels of vitamin E in some subjects.<sup>133</sup> In a larger study, comparing 30, 180, and 360 mg/day of orlistat with placebo, only the 360 mg dose of Orlistat produced significantly greater weight loss (4.74 0.38 kg) than placebo (2.98 0.38 kg) at 12 weeks. Gastrointestinal side effects were reported frequently and about twice as many subjects receiving Orlistat dropped out of the study compared to those taking placebo. A decrease in the blood levels for vitamins A, E, and D was observed in the subjects receiving Orlistat, but was not considered clinically significant by the investigators.<sup>134</sup> Orlistat, which may ultimately serve as a useful adjunct to diet therapy, has undergone Phase III testing and is currently under review by the FDA.

### HERBAL PREPARATIONS

The use of herbal preparations for obesity is prevalent in the United States. Although many useful medicines have been derived from herbs and other plants, claims of therapeutic benefit, especially with regard to obesity, often overstate the existing scientific evidence. Kelp for example, in the form of powder or tablets, is often advocated for the control of obesity because the iodine in kelp is thought to stimulate thyroid hormone production. However, such stimulation would only occur in persons with iodine deficiency and iodine deficiency is very rare in this age of iodized

salt.<sup>123</sup> Many herbal products contain multiple ingredients and are promoted based on anecdotal claims of weight loss. One such product currently being sold locally as a “dieters herbal combination” at a national drug store chain contains chickweed herb, safflower florets, burdock root, parsley herb, kelp, papaya leaves, licorice root, fennel seeds, echinacea purpurea herb, black walnut hulls, and hawthorn berries. The remedy was formulated by a “master herbalist” and the label recommends 4 to 6 capsules with water 30 minutes before each mealtime or prepared as a tea.

Reports of serious adverse effects associated with the use of herbal remedies for weight loss are increasingly common.<sup>127,135 136 137 138</sup> Because these products are considered “natural” and typically marketed as food supplements, consumers may assume incorrectly that they are safe and lacking of side effects. Interpretation of reports of adverse effects is fraught with difficulty because herbal preparations are occasionally mislabeled or, in some cases adulterated, and contain ingredients or quantities not listed in the labeling.<sup>139</sup> The Texas Department of Health for example, during an investigation of adverse events related to ephedrine-containing products, purchased a product labeled “no side effects” that listed wild Chinese ginseng as the only ingredient. Upon laboratory analysis, a single tablets was found to contain 45 mg of ephedrine and 20 mg of caffeine. The label on the product recommended users take five tablets, representing a total ephedrine dosage of about 11 times the usual recommended dosage in OTC bronchodilators, which contain 12.5 to 24 mg of ephedrine per dose.<sup>127</sup>

Ma-huang is a herbal product derived from plants of the *Ephedra* species that has been used in China for thousands of years and is promoted as a weight loss aid.<sup>123</sup> The herb is sold as a dietary aid and is therefore exempt from the rigorous testing for safety and efficacy that drugs must undergo. The active constituent is ephedrine. As discussed, although ephedrine is capable of inducing modest weight loss by virtue of its anorectic and thermogenic properties, its use is associated with substantial risk for serious side effects including liver injury and psychiatric disturbances.<sup>127,137,138</sup>

The addition of two Chinese herbs (*Stephania tetrandra* and



Magnolia officinalis) to a slimming regimen containing a mixture of Western medicines (fenfluramine, diethylpropion, meprobamate) was implicated with the development of interstitial fibrosis leading to acute renal failure.<sup>136</sup>

The blossoms of wall germander (*Teucrium chamaedrys*) have long been used in folk medicine for obesity. Preparations include herbal teas, a medicinal liquor of germander admixed with other herbs, and capsules containing powdered germander alone or mixed with green tea. Although the herb was assumed to be harmless, hepatotoxicity has been reported recently.<sup>135</sup>

The aforementioned reports underscore the fact that just because a product derives from a natural source does not necessarily mean it is safe. It is likely that many natural products possessing clinically useful anorexiant activity await discovery. Unfortunately, data regarding safety and efficacy for many naturopathic remedies is lacking. Therefore, until this data is available these remedies cannot be recommended.

## **OTHER AGENTS**

### **SIBUTRAMINE**

Sibutramine, a promising new agent that boosts brain levels of both norepinephrine and serotonin by blocking their reuptake, is under review by the FDA.<sup>140</sup> In a 12 week study doses ranging from 10 to 30 mg daily were shown to produce significantly greater weight loss than placebo in a recent 24-week double-blind trial.<sup>141</sup> Weintraub and colleagues compared two different daily doses of sibutramine with placebo and showed a dose-related effect on weight loss.<sup>142</sup> Patients who took 20 mg daily lost an average of 5.0 kg, compared to 2.9 kg with 5 mg daily, and 1.4 kg with placebo. Side effects associated with sibutramine treatment included difficulty sleeping, irritability, unusual impatience, and excitation.

### **PECTIN**

Pectin is a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or apple pomace and consists mainly of partially methoxylated polygalacturonic acids. Pectin is an adsorbant and bulk-forming agent often present in multi-ingredient preparations for the management of diarrhea, constipation, and obesity. Pectin has also been used to decrease the rate of

carbohydrate absorption in the dumping syndrome.<sup>143</sup> The results of a preliminary study indicate that pectin may serve as a useful adjuvant in the treatment of obesity by virtue of its ability to induce satiety via delayed gastric emptying. Fifteen grams of pectin administered with a meal slowed gastric emptying, induced satiety, and prolonged the time to the next meal in nine obese subjects. As pointed out by the authors, additional research is needed to define the effect of pectin on weight loss and to determine the adverse effect profile of long term pectin ingestion.<sup>144</sup>

### **BROMOCRIPTINE**

Bromocriptine is a dopamine agonist that has been shown to decrease body fat stores in experimental animals with little or no reduction in body weight or food intake.<sup>145</sup> Accordingly, Meier and colleagues treated 33 obese postmenopausal women and 15 men with poorly-controlled Type II diabetes mellitus with bromocriptine. The subjects received 1.25 mg or 2.5 mg daily for 10 weeks with no other interventions. Body fat, as estimated by skinfold measurement, was reduced by 11.7% in the non-diabetic subjects. In the diabetic subjects, body fat was also reduced but to a greater extent in those subjects taking antidiabetic pills for control of their diabetes. Hyperglycemia resolved in most of the diabetics allowing cessation of hypoglycemic drugs in some. The degree of weight loss was minimal in all patients and mild nausea was the only side effect reported.<sup>146</sup> Encouraged by these results, the same investigators randomized 17 obese subjects to bromocriptine (1.6 or 2.4 mg daily within 2 hours of awakening of a quick-release form of bromocriptine) or placebo. In addition, all subjects were instructed to follow a moderately-low calorie diet. After 18 weeks, the subjects receiving bromocriptine had lost 6.3 kg and those receiving placebo only lost about 1 kg. Treatment with bromocriptine was also associated with a greater reduction in body fat and improved glucose tolerance.<sup>147</sup> The way in which bromocriptine decreases fat stores and body weight and improves glucose tolerance is not known, but appetite suppression or a reduction of lipogenesis (the production of fat) have been proposed.<sup>146,147</sup> Although these data are promising, the use of bromocriptine cannot be recommended until more information about long-term safety and efficacy is available. Bromocriptine is not currently FDA-approved for the treatment of obesity, but phase III studies are under way.

### **NALTREXONE**

Endogenous opioids have been postulated to be involved in the control of food intake.<sup>148</sup> Although early studies

suggested a benefit,<sup>149 150</sup> other randomized controlled studies of the opioid-antagonist naltrexone in doses ranging from 50 mg to 300 mg daily failed to demonstrate a significant effect in terms of weight loss.<sup>151 152 153</sup> Moreover, elevations in liver enzymes and hepatotoxicity occurred during the course of several of these studies.

### **GROWTH HORMONE (SOMATOTROPIN)**

Growth hormone is secreted by the anterior pituitary and, in addition to promoting growth in children, possesses anabolic, lipolytic, and diabetogenic actions. Growth hormone also affects energy balance by stimulating energy expenditure. The shrinkage of lean body mass and the expansion of adipose tissue mass associated with aging appears to be related to a decline in the production of growth hormone. Growth hormone secretion is also suppressed in obese persons. The widespread availability of synthetic human growth hormone has allowed the evaluation of the effects of the hormone in a variety of conditions including obesity and aging.

In an effort to avert the loss of lean body mass that accompanies weight reduction programs for obesity, growth hormone appears to reduce body fat and preserve lean body mass.<sup>154</sup> Six months of growth hormone treatment (0.03 mg/kg of body weight injected subcutaneously at 8 a.m. three times weekly) reduced body fat mass and increased lean body mass significantly with no change in overall body weight in a small group of elderly men with reduced baseline growth hormone secretion.<sup>155</sup> Side effects, consistent with hypersomatotropism, included small increases in systolic blood pressure and fasting plasma glucose levels. In 12 obese women, randomly assigned to receive growth hormone (0.08 mg/kg intramuscularly three times weekly) or placebo, treatment with growth hormone was associated with a reduction in body fat and increased in lean body mass.<sup>156</sup>

Although these results are promising, growth hormone excess, as exemplified by acromegaly, adversely carbohydrate metabolism (inducing hyperinsulinemia, glucose intolerance, and diabetes mellitus), the musculoskeletal system (causing arthritis and arthralgia), and the cardiovascular system (producing hypertension, edema, and congestive heart failure).<sup>157</sup> Clearly, longer-term studies are needed to define fully the beneficial and toxic effects of growth hormone before treatment of both obese and elderly persons can be recommended.

### **ANABOLIC AND ADROGENIC STEROIDS**

Central fat distribution (android obesity, the “apple” shape) is an important risk factor for metabolic and cardiovascular disease in both men and women.<sup>5,6</sup> These health risks appear to be mostly mediated by increased visceral intraabdominal fat, rather than subcutaneously- distributed abdominal fat. Several factors influence abdominal fat distribution including age, smoking and alcohol consumption, and hormones. Visceral fat accumulation appears to be associated with lower levels of androgens in both men and women.<sup>158</sup> Accordingly, anabolic steroids have been tried in both obese men and obese post-menopausal women.

Oxandrolone reduced subcutaneous abdominal fat and produced favorable changes in visceral fat in middle-aged obese men. However, therapy was associated unfavorable changes in the serum lipid profiles manifested as a decrease in HDL cholesterol and an increase in LDL cholesterol.<sup>159</sup> Treatment with nandrolone deconoate decreased total body fat and increased lean body mass in obese postmenopausal women but was associated with increased visceral fat, unfavorable changes in serum lipids, and undesirable side effects. Side effects included darkening of facial and body hair, acne, rash, changes in sleep habits, breakthrough bleeding, and headache.<sup>160</sup>

### **HUMAN CHORIONIC GONADOTROPIN (HCG)**

Injections of hcG have been tried as an adjunct for weight loss. Touted benefits include weight loss beyond that resulting from dieting, a more attractive or normal distribution of fat, decreased hunger and discomfort associated with dieting. Although an early study suggested a benefit,<sup>161</sup> subsequent randomized and controlled studies have demonstrated absolutely no benefit from hcG.<sup>162 163 164</sup> The reported effectiveness of hcG-diet programs has been attributed to the caloric restriction, frequent physician contact, and the placebo effect.<sup>26</sup>

### **DEHYDROEPIANDROSTERONE (DHEA)**

Several steroidal drugs have been evaluated. Dehydroepiandrosterone (DHEA), a naturally occurring steroid precursor of both androgens and estrogens is being sold at health food stores and some pharmacies as a “food supplement”. It is being promoted to offset the effects of aging, even though it is not approved for any indication by the US Food and Drug Administration.<sup>167</sup> DHEA has been reported to have beneficial effects on obesity, diabetes mellitus, and serum lipids in animals. However, a

randomized controlled study has shown no benefit in obese humans.<sup>168</sup>

### **CHROMIUM PICOLINATE**

Chromium picolinate is the latest rage and is sold in health food outlets and pharmacies as an ingredient in numerous “fat burner” products. Chromium is an essential nutrient that appears to serve as a cofactor with insulin in the maintenance of normal metabolism. Chromium deficiency can lead to insulin resistance and dysfunctions in carbohydrate, protein, and fat metabolism.<sup>169</sup> Enthusiasm for chromium for weight loss stems from some evidence that suggested daily supplementation with 200-400 micrograms of chromium picolinate increases lean body mass, while decreasing the percentage of body fat.<sup>170</sup> In contrast, subsequent studies have failed to demonstrate a significant effect from chromium picolinate on body fat.<sup>171 172 173</sup> In the most recent of these, 95 active duty obese navy personnel were randomly assigned to receive 400 micrograms of chromium picolinate or placebo. This very well-controlled study found absolutely no difference in the magnitude of weight loss, percent body fat, or lean body mass between those who took chromium picolinate and those who took placebo after 16 weeks of treatment.<sup>173</sup>

### **PYRUVATE AND DIHYDROXYACETONE**

Pyruvate is another supplement that has recently gained attention. Marketers of nutritional supplements are promoting the product on the Internet and other media as a way to burn fat without reducing muscle mass. These claims, however, are based on studies conducted in animals and on some very preliminary data in humans. Studies in experimental animals suggest that the combination of pyruvate and dihydroxyacetone may prevent fat accumulation, without a deleterious effect on body protein stores.<sup>174 175</sup> In a series of studies from the University of Pittsburgh involving a small number of obese women, pyruvate with or without dihydroxyacetone appeared to enhance body fat and weight loss during caloric restriction and to inhibit weight regain after weight loss.<sup>176 177 178</sup> Subjects receiving the combination of pyruvate and dihydroxyacetone during severe caloric restriction lost an average of 1 kg (body weight) more than those receiving placebo during severe caloric restriction.<sup>176</sup> Subjects who received pyruvate alone, during moderate caloric restriction, lost an average of 1.6 kg more than subjects taking placebo during caloric restriction.<sup>177</sup> In obese women who had lost weight during caloric restriction, the combination (15 grams of pyruvate and 75 grams of dihydroxyacetone day as a

portion of daily carbohydrate energy intake) appeared to inhibit regain of body weight and the reaccumulation of body fat during subsequent refeeding with a high calorie diet.<sup>178</sup> Side effects attributable to pyruvate and dihydroxyacetone supplementation included diarrhea and borborygmus (rumbling in the bowels produced by gas). As noted by the authors, the mechanism by which pyruvate and dihydroxyacetone induce these changes in body composition has not been established, but may involve increased energy expenditure or promotion of fat oxidation. It is important to note that the pyruvate and dihydroxyacetone were administered in isocaloric amounts as a portion of the total daily carbohydrate energy intake. Therefore, the effects of simply adding these 3-carbon compounds to the diet like a vitamin supplement are not known. Although these studies are encouraging, further research is needed to determine the effect of these supplements on long-term weight loss and to define fully the adverse effect profile. Like most nutritional supplements, pyruvate is not considered a drug and is therefore not regulated by the FDA.

### **SUMMARY**

The ultimate cause of obesity is an imbalance between caloric intake and energy expenditure resulting from complex interactions between many genetic and environmental factors. Obesity is chronic disease that afflicts millions of people worldwide and contributes to substantial morbidity and mortality. A successful weight control program must balance caloric intake with energy expenditure. Since the time of Hippocrates, diet and exercise have been the mainstays for weight control. Successful control of weight requires permanent lifestyle changes that include adoption of a healthful low-fat diet and 30 minutes of moderate physical activity per day. Drugs appear to be an attractive prescription for many. However, until information about long term safety and efficacy is available, drugs cannot be recommended for routine use. Exciting recent discoveries have led to a greater understanding of the interplay between the genetic and environmental factors causing obesity and will undoubtedly lead to more effective therapies.

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