

Weight Loss Drugs: What's In and What's Out

The number of adults in the United States who are overweight or obese has increased dramatically over the last decade. The classification of overweight and obesity as defined by the National Institutes of Health is shown in Table 1. Using these definitions, an estimated 97.1 million adults, or more than one-half of American adults are overweight or obese according to data from the National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994).

Table 1. NIH Classification of Overweight and Obesity

CLASSIFICATION

BMI (kg/m²)

Underweight

< 18.5

Normal

18.5 – 24.9

Overweight

25.0 – 29.9

Obesity, Class I

30.0 – 34.9

Obesity, Class II

35.0 – 39.9

Extreme Obesity, Class III

3 40

Source: National Institutes of Health, National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. The evidence report. 1998.

Overweight and obesity are not simply cosmetic issues. Research has documented that obesity is a major risk factor for numerous chronic diseases including heart disease, type 2 diabetes, hypertension, stroke, certain cancers and osteoarthritis². Additionally, body weight and mortality are directly related in women³. The cost of obesity is enormous, and the direct and indirect costs have been estimated to be \$68.8 billion in 1990⁴. Over the years, different drugs have been used to treat obesity. The use of weight loss drugs has evolved over the years from being a primary treatment to being a useful adjunct to, but not a substitute for, changes in eating and physical activity. It is now generally agreed that the effectiveness of pharmacologic intervention depends on its use with appropriate dietary intervention, increased physical activity, and lifestyle change². Additionally, most clinicians today view obesity as a chronic condition requiring long-term intervention. Weight loss drugs are now being evaluated with a view towards more long-term use.

Pharmacologic therapy is not appropriate for everyone who is overweight or obese. The North American Association for the Study of Obesity lists the following subgroups of patients as appropriate for drug therapy⁵:

- Individuals with significant health risks or comorbidities who have tried conventional therapy without success.
- Individuals requiring surgery whose weight places them at high risk for the procedure.
- Individuals without existing comorbidities, who have tried conventional therapy without success and whose obesity puts them in a high-risk category.

The BMI values that correspond to the descriptions above are: a BMI \geq 30 with no concomitant obesity-related risk factors or diseases and a BMI \geq 27 with concomitant obesity-related risk factors or diseases⁶.

Pharmacological interventions are designed to contribute to an energy deficit through a variety of mechanisms. Some act on neurotransmitters in the brain to partially suppress appetite and as a result, reduce food consumption. Some drugs

are being investigated to assess if they have a thermogenic role. Still others are non-systemic and act at the level of the gastrointestinal tract.

When the drugs affect neurotransmitters, the systems targeted are the catecholaminergic and/or the serotonergic pathways. Specifically, the neurotransmitters affected include norepinephrine, epinephrine, and dopamine in the former pathway and serotonin in the latter pathway. When neurotransmitters are released, they can bind to their receptor site, be degraded by enzymes and/or be taken back up by the nerve that released them. When they are taken back up, it is referred to as "re-uptake." Drugs can increase the amount of neurotransmitters by increasing the amount that is released or blocking re-uptake.

Side effects noted with the use of weight loss drugs are related to the neurotransmitter pathway affected. Therefore, catecholaminergic drugs have side effects that include sweating, palpitations, dry mouth, increased nervousness and insomnia⁷. In addition, they can increase blood pressure. Individuals taking serotonergic drugs have reported gastrointestinal disturbances (nausea or diarrhea)⁷.

The Drug Enforcement Agency classifies drugs according to their abuse potential. Prescription weight loss drugs with a high abuse potential are listed as "Schedule II and Schedule III Agents." Those with the lowest are listed as "Schedule IV." Over-the-counter formulations are "Unscheduled Agents."

Catecholaminergic Agents

Table 2 lists catecholaminergic agents used in weight management. The Schedule II Agents, amphetamine and phenmetrazine HCL, have stimulant properties and a high potential for abuse; therefore, they are no longer recommended for obesity treatment⁸.

Clinical data for the Schedule III Agents, benzphetamine and phendimetrazine tartrate are limited. Additionally, they are approved for only short-term use⁶. Their abuse potential should strongly considered before they are prescribed for therapy.

The FDA reviewed a large body of data on catecholaminergic drug use in the treatment of obesity. Included in the study were the Schedule IV Agents listed in Table 2. The length of the studies was 12 to 20 weeks. The results of the analysis indicated that those taking a weight loss drug lost approximately 0.5 pounds more each week than those on placebo⁹.

Table 2. Catecholaminergic Agents

Drug

Trade Name

Schedule III Agents

Benzphetamine HCL

Phendimetrazine tartrate

Didrex[®];

Bontril[®];

Schedule IV Agents

Diethylpropion HCL

Mazindol HCL

Phentermine HCL

Phentermine Resin

Tenuate[®];

Sanorex®;

Fastin®;

Ionamin®;

Unscheduled (OTC) Agents

Phenylpropanolamine

Dexatrim®;

Acutrim®;

Studies with over-the-counter medications have shown them to be less effective than prescription drugs as studies extend to more than four weeks. A metaanalysis of phenylpropanolamine studies since 1985 indicated that individuals on phenylpropanolamine lost 0.46 pounds more than individuals on placebo by the end of the fourth week of treatment¹⁰. At the end of the studies, there was a 0.31-pound per week greater weight loss on phenylpropanolamine versus placebo. Interestingly, 80% of patients who use over-the-counter anorectics do so for four weeks or less¹⁰.

Serotonergic Agents

Serotonergic agents that have been used for obesity are listed in Table 3. These drugs are agonists and act by increasing the release of serotonin. Dexfenfluramine was the first antiobesity agent approved by the Food and Drug Administration for both weight loss and maintenance of weight loss. This was an important change, in line with the evolving view of obesity management.

Table 3. Serotonergic Agents

Drug

Trade Name

Fenfluramine

Pondimin®;

Dexfenfluramine

Redux®;

Dexfenfluramine is the dextro-stereoisomer of dl-fenfluramine and had fewer antidopaminergic and sympathomimetic actions and side effects than fenfluramine. In a yearlong study of fenfluramine, patients on the drug plus diet lost about 10% of their baseline weight. Those on diet alone lost 6.3% of their baseline weight. Plateauing of weight occurred after six months of therapy in one of the fenfluramine-treated groups. Weight regain occurred after 10 months in another of the fenfluramine-treated groups¹¹. In another long-term study, fenfluramine was used during a weight loss phase and during a maintenance phase. During the yearlong maintenance period, approximately one-third of patients maintained their weight loss, one third regained weight, and one-third withdrew from treatment¹².

A one-year dexfenfluramine study showed that patients in both the drug and placebo groups lost a significant amount of weight during the first six months. After six months, those on placebo regained weight and those on dexfenfluramine plateaued¹³. The authors concluded that the plateau reached after six months indicated that the action of the drug was not to promote additional weight loss but to avoid weight regain¹³.

A long-term study was also completed using a combination of fenfluramine and phentermine¹⁴. In this three and one-half yearlong study, most weight loss occurred during the initial six months, and a statistically significant maintenance of weight loss was detected at one year or more.

There have been problems noted with the serotonergic agonists, fenfluramine and dexfenfluramine. Primary pulmonary hypertension (PPH), a rare, often fatal progressive lung disease, is a side effect associated with the use of these drugs, especially when used for more than three months^{15,16}. The risk for PPH in obese individuals using these drugs for more

than three months has been calculated to be more than 30 times higher compared to nonusers¹⁵. The mechanism of action is unknown although several hypotheses have been advanced. These include serotonin-induced contraction of pulmonary arteries¹⁶, a direct vasoconstrictor effect through potassium-channel blockade, and pulmonary vasoconstriction¹⁵.

Fenfluramine and dexfenfluramine use has also been associated with valvular heart disease^{17,18}. A study by Wadden et al.¹⁸ indicated that after two years of treatment with the fenfluramine-phentermine combination, 30% of patients they studied met the criteria for valvular heart disease. On September 15, 1997, at the request of the FDA, manufacturers voluntarily removed fenfluramine and dexfenfluramine from the market.

Newer Drugs

On November 22, 1997, FDA approved sibutramine (trade name, Meridia[®]) for weight loss and maintenance of weight loss¹⁹. Sibutramine is a phenethylamine that inhibits the re-uptake of serotonin and norepinephrine²⁰. Unlike fenfluramine and dexfenfluramine, sibutramine does not cause the release of neurotransmitters, but appears to act through re-uptake inhibition. The effect is to increase the amount of serotonin at the synapse. It is classified as a Schedule IV drug, meaning that it has a low potential for abuse and dependence.

Due to sibutramine's catecholaminergic action, many of the side effects are similar to those seen when using other appetite suppressant drugs, including dry mouth, insomnia, constipation and decreased appetite²¹. Sibutramine also increases heart rate by three to six beats per minute²². As a result, it is considered prudent to monitor pulse carefully in patients on sibutramine. Sibutramine also has an effect on blood pressure, but the effect is complex. Weight loss can be expected to have a predictable effect in reducing blood pressure. A catecholaminergic agent is likely to increase blood pressure. In normotensives, sibutramine increased both systolic and diastolic blood pressure by a mean of two mm Hg. When used with mildly hypertensive obese patients, a reduction in blood pressure was observed which mirrored the placebo group. Therefore, the study showed that the benefit of weight loss on blood pressure could occur with sibutramine use²². Still, it is considered prudent to observe blood pressure carefully when patients take sibutramine²². Heart rate and blood pressure effects are generally seen in the first eight weeks of treatment.

In a six-month double-blind randomized placebo-controlled study testing the effects of sibutramine on body weight, groups receiving sibutramine lost significantly more weight than a placebo group²¹. The placebo group lost less than one percent of their initial body weight, while the group receiving the highest dose of sibutramine (30 mg) averaged a loss of more than nine percent of their initial body weight. When the drug was discontinued, weight regain occurred. The results of a 12-month study of sibutramine indicated that weight loss could be maintained over the long term by use of sibutramine²². Not all individuals respond to sibutramine. Clinicians can make a judgement about response to the drugs within four weeks of starting sibutramine treatment. Non-responders are those who fail to lose one percent of their body weight after four weeks of treatment²².

Animal research indicated that sibutramine's effect on weight occurred through a reduction in food intake and an increase in energy expenditure²³. A study in obese women demonstrated that sibutramine reduced total daily energy intakes compared to the placebo²⁴. Sibutramine's effects on resting metabolic rate are unclear, with research indicating an increase²⁵ and no effect²⁶ of sibutramine on metabolic rate.

A new weight loss agent, orlistat (trade name Xenical[®]) is a completely different drug compared to previous medications for weight loss. Orlistat is not an appetite suppressant, but acts directly on the gastrointestinal tract to inhibit fat absorption. Because its effect occurs at the level of the gastrointestinal tract, it is nonsystemic. Specifically, it inhibits enzymes that play a pivotal role in the digestion of dietary fat, gastric and pancreatic lipases. As a result, orlistat inhibits the breakdown and subsequent absorption of dietary fat²⁷.

The dose of orlistat is 120 mg three times daily administered with meals. Increasing the dose of orlistat does not significantly increase the efficacy of the drug. The percentage of fat excreted continues to be about 30% of ingested fat. In practical terms, if an individual is following a diet that has 30% of calories from fat, orlistat will reduce fat absorption by 30%, so that in effect, the individual would be following a diet with 20% of calories from fat.

Trials of orlistat showed that after one year, weight loss in the orlistat-treated groups was significantly greater than in the placebo group^{28,29,30}. Studies that extended to two years and switched from a weight loss to a weight maintenance diet demonstrated that orlistat resulted in less weight regain in treated groups^{28,30}. Orlistat also improved weight maintenance after conventional dieting³¹. Other beneficial effects of orlistat include improved the lipid profiles, fasting blood glucose, diastolic blood pressure and fasting insulin²⁸. Because orlistat interferes with fat digestion, there is some concern about its effect on fat-soluble vitamin absorption. No clinically significant changes were noted in mean plasma levels of the fat-soluble vitamins²⁸. Supplementation with fat-soluble vitamins is still recommended, however.

Orlistat's side effects are related to fat malabsorption and include flatus with discharge, abdominal pain, fecal urgency, and oily spotting³¹. These effects occurred early in treatment and usually resulted from a dietary fat intake beyond 30% of calories. Most resolved spontaneously³¹.

Drug Treatment: Pros and Cons

There are pros and cons to every drug treatment. Weight loss/weight management drugs have been found to aid in adherence to dietary regimens. They result in a significantly greater weight loss than diet alone. They may also improve risk profiles in obese individuals. On the negative side is the fact that not everyone responds to treatment. After discontinuation of the drug, weight regain occurs. There are side effects when drugs are used, and research continues to discover if there are long-term effects. It is well-known that there are no easy answers to the puzzle of obesity. Different individuals respond differently to different treatments. The goal of clinicians should be to match the best available treatment to the individual.

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