The Efficacy and Safety of Anorexiant Medication in the Treatment of Obesity: Implications for Managed Care Formularies

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ABSTRACT: This article reviews the efficacy and safety of anorexiant medications in the treatment of chronic obesity, using data gleaned from Medline literature searches, manufacturer product information, and scientific studies. The authors have focused on patient selection and placement of selected anorexiant medications on the formulary for a managed care organization. The review reveals that lifestyle changes in a structured diet and exercise program remain the cornerstone in the treatment of obesity. Motivated patients may benefit from a short-term trial of anorexiant agents. The withdrawal of both fenfluramine and dexfenfluramine from the market has resulted in limited therapeutic options, especially for high-risk patients. Sibutramine and other drugs may offer advantages over conventional drugs, though careful monitoring by the pharmacist for adverse effects and drug interactions is necessary. There are insufficient studies on long-term efficacy, safety, and impact on disease markers to warrant the addition of these agents to a managed care organization formulary at this time.

KEY WORDS: Anorexiant medication, Obesity, Efficacy, Managed care

Obesity is a chronic disease that increases morbidity and premature mortality from several chronic illnesses. The incidence of obesity is increasing, affecting one in three adults, and is especially prevalent among those in the lower socioeconomic classes who are most at risk for coronary heart disease. However, the risks and frequency of obesity must be differentiated from those patients who are simply overweight. In the United States there is an obsessive compulsion to lose weight, especially among young women, which may lead to risky health behaviors such as anorexia and bulimia, as well as depression.

CLASSIFICATION OF OBESITY

Several indices have been reported in the medical literature to classify obesity, including: weight-height index or ideal body weight (IBW); waist-to-hip ratio (W/H); and body mass index (BMI). For IBW (i.e., insurance tables on height, body frame, ideal weight), a patient is considered “overweight” at 19% above listed weight. There are few studies that demonstrate an increase of health risk for “overweight” patients. Other classifications include: 21%–41% over IBW equals mild obesity; 41%–100% over IBW equals moderate obesity; and >100% over IBW equals severe obesity. Some studies define obesity as a waist-to-hip ratio of greater than 0.8 in females and 1.0 in males.

The National Center for Health Statistics (NCHS) utilizes body mass index to classify obesity. Body mass index is thought to be a better correlate with fat content than IBW. The BMI is calculated by dividing the weight in kilograms by the height in meters squared (BMI = kg/m²). See Table 1 for estimated BMI. The NCHS defines overweight as a BMI greater than 27.3 in females and 27.8 in males. Each BMI
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Table 1. BMI vs. Height and Weight

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unit represents approximately 3 kg. The newer pharmacological agents utilize BMI as a criterion for treatment.

**OBESITY AS A RISK FACTOR**

There is a modest increase in mortality as weight increases, but it does not become a significant risk factor until the BMI of 26–28 is reached.1,2 A BMI greater than 30 appears to be an important risk factor in the development of hypertension, hyperlipidemia, and type II diabetes mellitus. The direct costs attributed to obesity for these disorders alone have been estimated in 1990 dollars at $38.2 billion.4 Obese patients are more than twice as likely to develop hypertension than patients of normal weight; the risk of type II diabetes mellitus increases five times with moderate obesity. Whether long-term weight loss can reduce health risks and mortality has yet to be determined.

The combination of hypertension, diabetes, and hyperlipidemia is known as “Syndrome X,”5 in which obesity can initiate a cycle of insulin resistance, glucose intolerance, hyperglycemia, disordered lipid metabolism, and vascular resistance. Central or abdominal obesity (“apple-shape”) appears to correlate with an increase in cardiovascular morbidity and mortality, especially in males. Sustained weight loss would be expected to improve control, slow disease progression, and perhaps lessen the long-term costs of chronic illnesses.

Obesity also has been shown to be a risk factor for colon, rectal, and prostate cancers in men and for gall bladder, breast, cervical, endometrial, and ovarian cancers in women, as well as for osteoarthritis, sleep apnea, gout, and cholelithiasis. Lifestyle changes—diet, exercise, behavior—should be recommended for primary prevention in this patient population.

**TREATMENT OF OBESITY**

Nonpharmacological treatments have targeted the goal of reaching ideal body weight with low-calorie diets, aggressive exercise programs, and peer group behavioral modification programs, with limited short-term results and rather poor long-term success. A successful weight-loss program has been defined as a 10% weight reduction that has been maintained for five years.6 This weight loss, if it can be maintained, can reduce blood pressure, improve the lipid profile, and decrease insulin resistance and blood glucose.7

Pharmacologic agents are mostly classified as either noradrenergic or serotonergic agents and have had modest short-term effects on weight loss as an adjunct to lifestyle modification behaviors. The noradrenergic agents are thought to act...
by thermogenesis, whereas the serotoninergic agents have a
direct effect on the weight control centers in the brain. The
generic name and usual dosage of these medications are
included in Table 2. The primary noradrenergic agents
include phenylpropanolamine, as well as the amphetamine
cogeners like diethylpropion, mazindol, and phentermine.
Lack of long-term efficacy and cardiovascular side effects limit
their use.

Drugs with primary serotoninergic activity include fluoxetine
and the recently withdrawn fenfluramines. Sibutramine ap-
pears to work by inhibiting the reuptake of both neurotrans-
mitters; unlike the fenfluramines, it does not enhance the
release of serotonin. Orlistat (Xenical) is an antiobesity drug
rather than an anorexiant, which produces weight loss by
interfering with the absorption of dietary fat. Olestra (Procter
and Gamble) now is being incorporated as a food supplement
in snack foods to decrease the intestinal absorption of fat;
excess consumption causes gastrointestinal side effects.
This review will summarize the current status of
fen/phen and dexfenfluramine and focus on clinical studies
demonstrating the efficacy and safety of newer agents such as
fluoxetine, sibutramine, and orlistat as an adjunctive treat-
ment of obesity.

DEXFENFLURAMINE AND
FENFLURAMINE/PHENTERMINE

Dexfenfluramine (DF) was the first anorexiant drug
approved by the Food and Drug Administration (FDA) for
long-term use (12 months). Fenfluramine was usually com-
bined with phentermine and heavily utilized and marketed in
weight-loss clinics nationwide as fen/phen. However, these
drugs were voluntarily withdrawn from the market by Wyeth-
Ayerst in 1997 after reports of serious adverse effects.
The attractions of the fen/phen combination or DF alone
were their long-term efficacy and apparent safety in a group
of high-risk obese patients with hypertension and/or diabetes.
Patients on the fen/phen combination regimen lost an average
of 15.9% of initial body weight, compared to a loss of 4.9% in
the control group at 28 weeks. Approximately one-half of
those patients who completed the study at four years were
able to maintain a weight loss of 10% from initial body
weight.8

Dexfenfluramine was comparable in efficacy to the nor-
adrenergic agents in short-term studies and was better tolerat-
ed. In longer-term studies10-12 DF doubled the weight loss in
comparison to a placebo after six or 12 months. DF was not
indicated beyond one year, and most patients regained weight
within two months of discontinuing their use of DF.
In several studies13-17 DF caused favorable changes in dis-
ease markers such as blood pressure, blood glucose, insulin
sensitivity, and glycosylated hemoglobin, which appeared to
be clinically significant in the short term and independent of
weight loss. However, these modest benefits were lost when
patients regained weight after drug discontinuation.18

The fen/phen combination was generally well tolerated,
with only 15.7% of all patients dropping out during the
active treatment phase; side effects—mostly dry mouth and
sleep disturbance—were self-limited and moderated over four
weeks with continued therapy.

Similarly, dexfenfluramine was well tolerated in clinical
trials with less than 7% of patients dropping out due to
adverse effects, compared to 5% in the placebo group. Com-
mon self-limited adverse effects included diarrhea (17.5%),
dry mouth (12.5%), and insomnia and drowsiness (7.1%).19
One of the rare, though more serious, adverse effects
with both fenfluramine and dexfenfluramine was an increase
in the incidence of primary pulmonary hypertension (PPH).10
The relative risk of developing PPH increased after more
than three months of treatment. Marker symptoms included
decrease in exercise tolerance and presence of dyspnea, syn-
cope, lower extremity edema, or angina.20 While the inci-
dence was rare, the four-year mortality of PPH was 45%. In
one case report, a healthy 29-year-old woman died of PPH
eight months after taking fen/phen for less than one month.21

In addition to PPH, reports of regurgitant valvular heart
damage in patients with no history of cardiac disease led to
the withdrawal of both drugs from the market. Connolly et
al.22 identified valvular changes by echocardiography in 24
healthy female patients who were maintained on the fen/phen
combination for an average of one year. These patients pre-
vented with shortness of breath, ankle swelling, fatigue, or a
heart murmur. Several of these patients had evidence of PPH,
and some required heart surgery.

Additional case reports on fen/phen24 and dexfen-
fluramine25 also have been reported. Pharmacist-initiated med-
ication histories are important, since those patients with val-
ular damage may be susceptible to bacterial endocarditis
during certain procedures in the future. The Centers for Dis-
ease Control (CDC), FDA, and National Institutes of Health
(NIH), in consultation with professional organizations, have
published26 the following guidelines for patients prescribed
either DF or the fen/phen combination:

▲ Patients should see their physicians for a detailed medical
history and physical examination. An echocardiogram is indi-
cated in the case of heart murmur or shortness of breath.
▲ If patients are without murmur or symptoms, an echocar-
diogram is not necessary immediately but should be ordered
if the patient will be undergoing any dental, medical, or sur-
gical procedures in the future.

FLUOXETINE (PROZAC)

Fluoxetine has become the surrogate anorexiant agent with
primary serotoninergic activity replacing DF and fenfluramine.
Fluoxetine alone or in combination with phentermine (pro/phen)
is neither FDA approved nor sanctioned by the pharmaceuti-
cal manufacturers for the treatment of obesity; however, flu-
oxetine is FDA approved for atypical eating disorders.
Fluoxetine in a daily dose of 60 mg over eight weeks has been shown to be more effective than placebo in normal obese and diabetic obese patients, however, most of the weight is regained. Goldstein et al. compared fluoxetine (60 mg daily) with placebo in 458 patients in a 52-week double-blind randomized study. The treatment group lost more weight at 28 weeks than the placebo group, but there was no difference at 52 weeks.

Gray studied 36 obese type II diabetic patients who were placed on a 1,200-calorie diabetic diet and either placebo or fluoxetine (60 mg/day) and followed for 24 weeks. The treatment group both lost more weight (9.3 pounds vs. 1.9 pounds) and experienced a greater decrease in the insulin dose (47% vs. 19%) than the placebo group: glycosylated hemoglobin and fasting blood glucose did not differ at the conclusion of the study. In a similar study over one year, the fluoxetine group lost more weight than the placebo group at three, six, nine, and 12 months; median fasting blood glucose and glycosylated hemoglobin differed from the placebo group only at three and six months. Connolly et al. reported similar results on weight loss and glycosylated hemoglobin in a six-month study. The increase in insulin sensitivity is thought to be independent of weight loss.

The use of fluoxetine and phentermine (pro/phen) has been popularized since the withdrawal of fenfluramine and its dextro isomer, and due to anecdotal clinical experiences shared in the medical literature. Anchors suggested using fluoxetine as a safe alternative. In his practice, 557 patients lost weight on a dose of 10 mg of fluoxetine and 30 mg of phentermine, and they tolerated the medications. Most patients appeared to need long-term therapy to maintain the weight loss. In comparison to studies of fluoxetine alone, the dose is extremely low but advisable due to a potential drug interaction (see Figure 1). This combination needs scientific validation before widespread incorporation into a managed care formulary or protocol.

Because higher doses of fluoxetine are required to exert an anorexiant effect, more side effects would be expected. However, in most studies the higher dose was well tolerated—even in elderly patients with type II diabetes—with few dropouts due to side effects. The most common dose-related side effects include asthma, somnolence, and sweating. Fluoxetine can cause a photosensitivity reaction, so the pharmacist must counsel the patient on the importance of sunscreen protection.

A toxic reaction has been reported with the inadvertent combination of fluoxetine and phentermine. Eight days after discontinuing the antidepressant (20 mg/day) the patient was started on phentermine by another physician. The patient experienced jitteriness, palpitations, tremors, stomach cramps, and dry eyes; vital signs were normal with hyperreflexia noted. The symptoms were relieved by low-dose lorazepam. One theory is that fluoxetine (and its active metabolites) inhibited the cytochrome P450 enzyme system, causing an increase in phentermine levels and sympathetic nervous system overactivity.

Fluoxetine does not appear to cause the serious adverse effects of PPH or valvular damage common with the fenflu-ramines. A serious adverse reaction can occur if fluoxetine is combined with monoamine oxidase inhibitors (MAOIs). There also is concern that using fluoxetine (or sibutramine) in patients without a neurotransmitter deficiency (i.e., depression) may result in a serotonin excess syndrome. Like DF and sibutramine, fluoxetine in combination with other drugs containing serotonin agonist or causing mimetic activity may cause such a syndrome, which is manifested by anxiety, agitation, hypomania, excitement, ataxia, confusion, or disorientation. If symptoms are present, the physician should be notified and the drugs discontinued immediately.

**SIBUTRAMINE**

Sibutramine (Meridia) was approved in February 1998 for the treatment of obesity. It is recommended at an initial dose of 10 mg for patients with a BMI ≥ 30, or ≥ 27 in the presence of other risk factors. For patients who do not tolerate the 10 mg dose, 5 mg is recommended, though the response is diminished. The usual maintenance dose is 15 mg. Sibutramine is approved for use up to 12 months.

Sibutramine has been shown to produce dose-related weight loss in several clinical trials. Bray et al. randomized 1,047 obese patients to receive either sibutramine at varying doses or placebo for 24 weeks. Mean weight loss at 24 weeks is shown in Figure 2 for each of the doses investigated. The majority of the weight loss occurred in the first 12 weeks of the trial, though patients receiving the higher doses (10-30 mg) continued to lose weight until the study concluded at 24 weeks.

Jones et al. randomized 485 patients to receive daily doses of 10 mg, 15 mg, or placebo for one year. At the end of
the trial, patients taking 10 mg lost an average of 4.8 kg, while patients taking 15 mg lost 6.1 kg. In a further analysis of this study, Lean et al. reported that 30% of patients taking 10 mg and 39% of patients taking 15 mg experienced a weight loss of 10% of body weight. The efficacy of the drug often can be assessed by initial response to therapy; if the patient has not lost four pounds or 1% of body weight at four weeks, the chances of the drug's succeeding are diminished.

The effect of sibutramine on disease markers for diabetes and hyperlipidemia appears to be less than reported with the fenfluramines and fluoxetine. The effect of sibutramine (15 mg) on hemoglobin A1c did not differ significantly from placebo in overweight noninsulin-dependent diabetics after 12 weeks. In clinical trials lasting 12–52 weeks, sibutramine appears to have a neutral effect on both blood glucose and the lipid profile, though it can increase blood pressure as discussed below.

In placebo-controlled clinical trials, 9% of patients withdrew from the studies due to adverse effects. The incidence of common adverse effects greater than placebo was dry mouth (13%), headache (11.7%), insomnia (6.2%), and constipation (5.5%). In premarketing trials, no cases of PPH were reported; however, it is not known whether this drug may be a causative agent. Sibutramine does not appear to cause valvular heart disease, unlike the fenfluramines. Prudent monitoring for cardio-respiratory symptoms by the pharmacist is suggested until more clinical experience is gained with this drug.

Sibutramine has also been associated with adverse effects on blood pressure and heart rate. In clinical trials, most patients experienced minor changes in both parameters; however, at doses of 15 mg per day, approximately 13% of patients experienced an increase of systolic blood pressure of more than 15 mm Hg, and 17% experienced an increase in diastolic blood pressure of more than 10 mm Hg.

Sibutramine should not be used concurrently with other sympathomimetic drugs or used in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, stroke, or uncontrolled hypertension. The pharmacist should monitor the blood pressure and pulse in all patients at time of refill.

Sibutramine is contraindicated in patients taking monoamine oxidase inhibitors and other centrally acting appetite suppressants. Due to the risk of serotonin syndrome, sibutramine, like fluoxetine and the fenfluramines, should not be used with the drugs listed in Figure 1. It also may interact with agents that inhibit the CYP 3A4 enzyme; however, the effect appears minimal.

**ORLISTAT**

Orlistat (Xenical) selectively inhibits gastric and pancreatic lipases that digest dietary fat and has little or no activity on amylase, trypsin, chymotrypsin, and phospholipases. At a dose of 120 mg three times daily, it inhibits the absorption of dietary fat by approximately 30%.

The efficacy of orlistat was measured in a double-blind, placebo-controlled parallel group study over 12 months. At six months, weight loss in the treatment group (8.6 kg) was greater than placebo (5.5 kg); at 12 months the orlistat group maintained weight loss while the placebo group relapsed and regained weight. There was a minor decrease in low-density lipoproteins, with no impact on total cholesterol or high-density lipoproteins.

Due to orlistat's unique mechanism of action, fewer systemic adverse effects would be expected; however, localized GI effects occur at a much higher rate. In one study, the percentage of subjects experiencing adverse gastrointestinal effects was: 34% fatty/oily evacuation; 20% increased defecation; and 15% soft or liquid stools. There appears to be a dose-related increase in adverse effects, especially if fat intake in the diet is not reduced.

Orlistat also may decrease the absorption of fat-soluble vitamins. Melia et al. reported that orlistat significantly reduced vitamin E absorption (though not vitamin A) at therapeutic doses. James et al. also reported decreases of both vitamin E (alpha-tocopherol) and beta carotene after one year on orlistat. Vitamin supplementation may become necessary with long-term use. Fortunately, orlistat does not appear to interact with common drugs such as phenytoin, warfarin, digoxin, oral contraceptives, glyburide, pravastatin, or slow-release nifedipine.

Though orlistat was initially approved by an FDA advisory committee in 1997, the manufacturer elected not to market the drug until more studies on potential adverse effects are known.
MANAGED CARE FORMULARY: THUMBS UP OR THUMBS DOWN?

Each MCO must develop its own policy and protocol on the most cost-effective treatment for obesity. The MCO must educate and identify those obese patients who are truly at risk for more aggressive therapeutic interventions.

To enhance the chances for success, the patient must be motivated to make lifetime lifestyle changes in diet, exercise, and behavior. The MCO must have a structured, well-organized weight-control program before even considering pharmacological therapy. The patient outcome goals must be realistic; a consistent moderate exercise plan coupled with a reasonable caloric restriction (1200–1500 kcal/day) in order to lose and maintain loss of 10% to 15% of initial body weight is recommended. Frequent follow-up visits with the nutritionist are recommended to reinforce lifestyle behaviors.

Subgroups of motivated patients may benefit from short-term therapy for initial weight loss as an adjunct to lifestyle changes; however, routine use of anorexiant agents is not recommended. If patients do not respond with a four-pound weight loss during the first month of any anorexiant therapy, the physician should consider discontinuing the use of the drug. Patient education should include the limited role of anorexiant agents in the weight-control program; if anorexiant agents are prescribed or used—including over-the-counter (OTC) or herbal therapies, either within or outside the plan—the pharmacist needs to monitor the patient for drug efficacy and toxicity.

Fluoxetine is probably already on the MCO formulary; in higher-than-usual prescribed doses, it may be effective in achieving short-term weight loss for truly obese patients with hypertension or diabetes, especially if the patient has a documented history of depression. The use of this drug alone should be considered experimental for this indication, and combination with other agents is not recommended due to potential for adverse effects and drug interactions.

Since its effectiveness in sustaining long-term weight loss is modest in limited clinical studies, with no favorable impact on disease markers, sibutramine is not recommended for addition to the MCO formulary at this time. Caution is advised in prescribing this drug for patients with hypertension, especially at therapeutic doses of 10–15 mg/day. As with fluoxetine, the pharmacist must review the profile for potential drug interactions. Orlistat, if its GI side effects can be tolerated, shows promise, but it is not FDA approved for use at this time.

If any anorexiant agents are approved by the Pharmacy and Therapeutics Committee, these medications should be considered for "restricted status" with specific utilization guidelines. Fluoxetine or sibutramine should not be used in combination with other anorexiant drugs, including OTC and herbal remedies. Efficacy and safety issues should be reassessed at one, three, and six months of therapy. Treatment beyond 12 months is not approved.

To maximize compliance with the more important lifestyle changes, the MCO may need to institute a higher copay for anorexiant agents or provide for a contract on expectations between the patient and the clinician prior to initiating therapy.

▲ References