

**UCLA**  
**Nutrition Bytes**

**Title**

Phen/Fen

**Permalink**

<https://escholarship.org/uc/item/61z0v85b>

**Journal**

Nutrition Bytes, 3(2)

**ISSN**

1548-4327

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**Publication Date**

1997

Peer reviewed

Obesity is the second leading cause of preventable death in the United States, behind only cigarette smoking (2). In addition obesity is a major risk factor for diabetes mellitus, some cancers, and cardiovascular disease, and it is responsible for nearly 300,000 deaths annually in the United States(1). In the United States approximately 15% of the population is at increased health risk because of obesity and the direct and indirect health care costs associated with obesity are in the billions of dollars annually.

In the past, weight loss plans have tried to modify various factors in patients' lives including diet, exercise patterns, and behavior in order to achieve weight loss and improve health. Loss of roughly 10% of body mass has been shown to improve the health risk factors associated with obesity. Even loss of as little as 5% of body weight may improve medical conditions associated with obesity such as insulin resistance, hyperlipidemia, and hypertension(3). Unfortunately these traditional interventions to reduce body weight have been ineffective and there has been renewed interest in treatment of obesity with drug therapy. The most current trend in pharmacological treatment of obesity is the combination of the drugs phentermine and fenfluramine or phen/fen.

At one time amphetamines were popular prescription drugs for weight control because of their ability to suppress appetite. Amphetamines work by increasing the amount of serotonin present in the synaptic cleft by not only inhibiting re-uptake of the serotonin but also by triggering the release of serotonin from the pre-synaptic nerve terminal(8). It was theorized that dietary starch is converted to sugar, sugar stimulates the pancreas to release insulin, insulin raises brain levels of the amino acid tryptophan, tryptophan is a precursor of serotonin, and serotonin regulates mood, producing a sense of well being(4). As a result of increasing the amount of serotonin at the synapse a sense of well being or fullness is created thus suppressing appetite. Unfortunately amphetamines were very addictive, so other similar drugs were created such as fenfluramine. These drugs produced many of the same results but did not possess some of the bad side effects that amphetamines did. According to Weintraub (10) fenfluramine led to a greater weight loss than placebo. Similarly, according to Hudson (6) patients treated with fenfluramine lost 10.2% of their baseline weight. Fenfluramine like other serotonergic drugs does cause some side effects. These side effects include gastrointestinal disturbances, drowsiness, lethargy, dry mouth, anxiety, agitation, and possible feelings of depression upon cessation of treatment(9). The major problem with fenfluramine is the fact that weight loss slows after several months, is minimal by the 6th to 10th months, and is maintained only so long as the drug is taken, with immediate reversal of the weight loss upon drug discontinuation.

Phentermine is chemically similar to fenfluramine but its method of action and effects are much different. Phentermine works by increasing the dopaminergic activity in the hypothalamus by blocking the re-uptake of dopamine in the synapse(7). Activating this catecholaminergic pathway results in stimulation and appetite suppression as opposed to the almost depressing effects of fenfluramine. In double blind trials, phentermine was found to be more effective than placebo in promoting weight loss in patients with obesity (9). The side effects of phentermine reflect the mild sympathomimetic and stimulant

properties of the drug and include insomnia, nervousness, irritability, headache, increased blood pressure, dizziness, and nausea(3).

In 1992 Dr. Michael Wientraub used in combination phentermine and fenfluramine in a four year clinical trial. It was hoped that this combination would give the anorectic effects of both of the drugs, yet allow lower dosages of each in order to avoid or minimize the side effects. The results were outstanding. Using a dose of 60mg of fenfluramine and 15mg of phentermine the treatment group lost three times as much weight as the placebo group(10). Additionally the participants who continued with the medications continuously lost an average of 16% of their body weight. Most importantly Weintraub's four year study showed that long term use of anti-obesity drugs was feasible because of limited side effects and little or no evidence of abuse or addiction

Although it achieved its goal of appetite suppression and weight loss, some problems with the diet plan have surfaced. When patients were removed from the medication, they regained an average of 80% of the weight they had lost (5). This implied that to maintain the weight loss patients had to continue to use the phen/fen indefinitely. In the New England Journal of Medicine an article was published relating the use of phen/fen to primary pulmonary hypertension in slightly higher than background levels(1). In addition risk factors such as smoking, pulmonary hypertension, drug abuse, and cirrhosis of the liver can lead to greater side effects or complications when taking phen/fen.

In my opinion the most serious problems related to phen/fen are its unregulated distribution and the cash driven incentive for doctors to prescribe it. The patients most likely to benefit from the use of phen/fen are those whose body mass indexes are greater than 30 and on whom nonpharmacologic interventions have been unsuccessful (11). These BMI's correspond to patients that are 5ft 6in. tall and who weigh between 167 and 186 pounds. Unfortunately many patients with little or no weight problems at all are taking phen/fen to improve their appearance. In order to research the topic I attended a phen/fen seminar on March 22 in Los Alamitos, California. The seminar was roughly 2.5 hours long and consisted of about 2 hours of diet information (food pyramid, the zone) and about .5 hours of discussion about phen/fen (risks, benefits, etc.). The seminar concluded with a five minute visit individually with the lecturing physician and subsequent prescription of phen/fen for each seminar participant regardless of their weight, body mass index, or pre-existing conditions. I spoke to one patient who was warned about taking phen/fen by the physician yet was subsequently prescribed phen/fen anyway. These seminars are not uncommon and are leading to excessive and inappropriate prescription of the medication. The driving force behind these seminars and many other physicians prescribing phen/fen is unfortunately money. Speaking with my preceptor, he commented that his partner makes an additional 7-8,000 dollars a month while prescribing phen/fen. My preceptor also mentioned that pharmaceutical companies making phen/fen are offering large bonuses to attract family practitioners to start prescribing their products.

Alone or in combination phentermine and fenfluramine have been shown to be effective at suppressing appetite and aiding in weight loss by the mechanisms previously

described. Unfortunately several problems have arisen as a result of inappropriate prescription and incentive medicine. In my opinion these products can be very safe and useful when used appropriately in helping to lower the risk of cardiovascular disease, diabetes mellitus, and other diseases that are associated with obesity.

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