ORIGINAL ARTICLE

LONG-TERM FOLLOW-UP OF A CLINICAL TRIAL OF ANOREXIANT DRUGS

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In this paper we describe the follow-up of patients who participated in a weight control study (1), which we had found that the combination of phentermine and fenfluramine was as effective as twice the dose of either drug alone and was more effective than placebo. Medications were given for 16 weeks then tapered over 4 further weeks.

Since obesity is a chronic condition with a high relapse rate, long term follow-up is necessary to evaluate success of the treatment program. Additionally, knowing what happened to the participants after the study may give a better view of how to administer anorexiant drugs properly. Studies of weight-control using several anorexiant drugs (including phentermine (2), mazindol (3,4), diethylpropion (5), and fenfluramine (6,7)) have all reported that participants regain a substantial percentage of their lost weight after discontinuing active medications.

In obese patients, drug compliance and diet adherence play vital roles in determining the outcome of treatment. To obtain data on these points in the follow-up study we paid particular attention to the feelings of the participants toward anorexiant drugs, diet and the overall study. Additionally, we determine the time when the participants started to gain weight, since such information may indicate the need for drug-retreatment and its timing.

PARTICIPANTS AND STUDY DESIGN

81 participants of both sexes, 130 to 180 percent of ideal body weight by the Metropolitan Life Tables, were enrolled in the initial study(1). The study was a double-blind, parallel group comparison of phentermine resin (delayed release) 30 mg in the morning; fenfluramine 20 mg three times a day; placebo, and a combination of phentermine resin 15 mg in the morning and fenfluramine 30 mg before the evening meal. All participants had a three-week period of diet only followed by 16 weeks of drug treatment plus diet, 4 weeks of tapering off the medication, and finally a four-week follow-up period of all medications. At a follow-up visit one month off medication, mean weight increased slightly in three treatment groups (combination, 0.4 kg; phentermine, 0.1 kg; placebo, 0.2 kg) but decreased further in the fenfluramine-group (0.1 kg).

The long-term follow-up study was done 7 months after the initial follow-up off medication. Participants were asked to come to a special clinic for interview and measurement of weight and blood pressure and to fill in a questionnaire about current weight, diet adherence (measured by a visual analog scale), any anorexiant drugs taken after the end of study and their opinion of the medications. The participants who did not attend the clinic were asked to mail in the questionnaire.

Statistical analyses were performed on the completed questionnaires. Since geometric mean is the best measure of central tendency in distributions having a skewness as usually found in weight-control studies, we used it in calculations of weight changes.

RESULTS

Respondents

Of the 81 participants, 32 attended the clinic, and 26 responded by mailing in the questionnaires. One participant sent in a blank sheet. Thus, these analyses include 71.6% of the total study population. Missing data included 8 participants who had moved without leaving a forwarding

address and 15 who did not respond despite repeated attempts urging to at least mail in the questionnaire. The numbers of participants who responded to this follow-up study in each treatment group are as follows: 76.2% in the combination group, 30% in the phentermine group, 65% in the fenfluramine group, and 60% in the placebo group.

Weight gain

84.2% of the respondents gained some weight after the completion of the formal drug study period. 21% regained or surpassed their pre-study weights. Most of the participants started to gain weight gradually after the completion of the study. During Thanksgiving to Christmas, the magnitude of weight gain increased greatly: 13 participants gained back 5 to 10 kgs and 2 other participants gained more than 10 kgs in the five-week holiday period.

The mean (±S.E.M.) percentage weight regain were: 9.7 ±2.25 in the combination group; 8.39 ± 1.4 in the phentermine group; 4.24 ± 2.27 in the fenfluramine group, and 1.29 ± 1.81 in the placebo group. These values are calculated as percent of weight regained from week 20. The data shown in Table 1 indicate that participants in active treatment groups lost more weight during the study than those patients on placebo. Approximately 16% of participants successfully maintained the newly established post-study body weight. There is no significant difference between the number of participants gaining weight in the four treatment groups (Chi-Square, X^2 = 0.94). The average of percent weight gain to original weight lost during the study, in the placebo and fenfluramine groups were less than in the phentermine and combination groups. Of those participants who regain weight , 33.3% in the placebo group, 44.4% in the fenfluramine group, 14.3% in the phentermine group, and 6.3% in the combination group regained 10% of the original weight lost at week 20. Participants in the phentermine and combination groups lost more weight and gained back more than those in the fenfluramine and placebo groups, although statistically significant differences were not demonstrated.

Table 1. Percentage of weight regained compared to original weight loss at week 20

Treatment (Respondents)	Numbers of patients gaining weight after week 10	Geometric mean % weight gain
Placebo (N = 12)	9	7,6
Fenfluramine (N = 13)	9	6,9
Phentermine (N = 16)	14	31,2
Combination (N = 16)	16	38,0

Participants' view of medications

We have already reported that side effects experienced by the participants in each active treatment group were not excessive and were least in the combination group (1) In this study the participants were also asked to give their opinion about the study medications, physicians and diets.

11 of 12 in the placebo group, 13 of 16 in the fenfluramine group, 4 of 16 in the phentermine group, and 3 of 16 in the combination group had negative feelings about the medications. In Table 2, we summarize the various reasons given by respondents for disliking the medications.

After the completion of the study, 6 participants took anorexiant drugs for a time but then stopped, 1 participant is still taking them at the time of follow-up. The drugs used by the patients included phenylpropanolamine (Control^{R}, Dexatrim^{R}, PVM, Dexa-diet II^{R}), fenfluramine (Pondomin^{R}), and phentermine. All of the participants who took OTC anorexiant drugs (e.g.phenylpropanolamine) found them to be ineffective. One participant who continued to take the combination of phentermine and fenfluramine thought that the medication really helped to control her appetite. Those participants who favored the study medications would like to be on the medications again. However, all of them felt that the anorexiant drugs should only be used under close supervision.

All participants indicated that the study diet was easy to adhere to, because it was devised individually (18 kcal/kilogram ideal body weight)

Table 2. Patients with negative attitude to the study medications.

Treatment group	Numbers of patients with negative feelings	Reasons for disliking
Placebo	11/12	10-ineffective 1-side effects
Fenfluramine	10/13	3-ineffective 3-tolerance & side effects 4-side effects
Phentermine	4/16	1-tolerance 2-side effects 1-side effects & ineffective
Combination	3/16	3-side effects

and based on the patients' preferences. However, only 1 out of 57 participants estimated that she was 90% faithful in following the diet as measured by visual analog scale, 14 participants estimated diet-adherence in the 50%-75% range, the remainder were under 25%.

DISCUSSION

Opinions regarding the value of anorexiant drugs in the treatment of obesity vary greatly (8). Some physicians believe that anorexiants are a valuable adjunct to other modes of therapy, such as diet and behavioral modification, while others feel that they are not effective and too dangerous to be generally recommended. In one recent paper (9), the authors stated that adding pharmacotherapy to behavior modification compromises the long-term effects of the latter treatment.

Continued weight problem may exist despite drug treatment either because the drugs are ineffective, or because they are only of short-term benefit, or because they are not being used properly. In order to clarify the issue, these questions must be considered: (1) are anorexiant drugs really effective?, (2) if so, what happens to the weight loss when the drugs are discontinued?; and (3) how could the drugs be administered properly to achieve long-term benefit? Several studies have indicated that ampheta-

mine derivatives including phentermine (2, 10-12), fenfluramine (13, 14), and diethylpropion (13, 15) and the non-amphetamine derivative, mazindol (16-18) are effective in producing weight loss.

We can conclude from our previous study that the use of a combination of phentermine and fenfluramine is a useful approach for achieving better therapeutic effect with less undesirable side effects The rationale for this approach rested on a variety of separate animal and human studies (20-23). Amphetamines and other drugs with similar chemical structure have been shown to inhibit the initiation of feeding. Although the chemical structure of fenfluramine is similar to that of amphetamine, it seems to act by increasing satiety or causing earlier termination of feeding (21, 22) Unlike the other phenylethylamines which demonstrate CNS stimulant activity, fenfluramine's major side effects are sedation and occasionally depression. Fenfluramine has few cardiovascular effects, while the other stimulant anorectics may occasionally increase blood pressure and pulse. Therefore, combination of phentermine and fenfluramine might be synergistic in therapeutic effect but antagonistic in adverse effects.

The data from our study as well as the other studies (2-7) indicate that most of the participants regained substantial weight sometime after the medications are discontinued, though the motivation for losing weight still existed. In this study, participants in the group who lost more weight (phentermine and combination groups) tended to gain back more. These findings may be due to the rebound phenomenon which often occurs in medical practice, since body weight seems to be regulated by a set point mechanism in much the same way as body temperature (24). Several studies in animals (25-28) and man (29-32) have suggested that the body weight is maintained within certain limits even when subjected to different environmental and physiological settings. If this set-point hypothesis holds true, regaining of weight can occur with any form of obesity treatment. In fact, behavior-therapy patients also regained weight substantially after treatment (8) as do patients having an intestinal bypass reattached (33).

All forms of obesity treatment, ranging from the least aggressive method of diet-therapy to the most aggressive one of intestinal bypass

surgery, are of some value, if they are used properly in the appropriate patients. Since obesity is a complex condition with multiple causes and underlying pathophysiological conditions (8), the outcome of treatment depends on several factors. Pharmacotherapy, if used properly, is certainly useful both as single or adjunctive therapy.

If one measures anorexiant effect by continuous weight loss, tolerance to anorexiant effect might be considered to have occurred. But if the maintenance of weight loss or the prevention of regaining lost weight are considered to be the goal of therapy, treatment would still be useful. At the time of follow-up most of the participants in our study still weight less than original weight; and the results from test meal study indicated that the total calorie intake was still decreased after the medications have been discontinued for four weeks. There have been some studies (34, 35) with the successful long-term treatment with anorexiant drugs covering more than one year.

In our study, most participants reported substantial weight gain during the holiday period, with a failure to adhere to the diet even though they thought it was easy to follow. Lack of appetite suppressing formerly induced by anorexiant drugs may not be responsible for the failure of diet adherence. It may be necessary in the long run to readminister drug and diet re-enforcement prophylactically at the beginning of the holiday periods.

In this study phentermine and the drug combination of phentermine and fenfluramine were well accepted by the participants. All those who favored these drugs indicated that they would like to be on them again to help them control their weight. However, fenfluramine was not tolerated well by most of the participants receiving this drug alone. Fenfluramine, has been widely prescribed and well accepted in most European countries. Cultural factors may play an important role in this difference. Since drug compliance significantly determines the outcome of treatment, anorexiant drugs must be well accepted by the patients.

Behavior therapy has recently become one of the most popular approaches to the treatment of obesity. However, it also has several drawbacks. The loyalty of adherents to behavior modification is crucial to

success of treatment. It requires well-trained personnel and therefore cannot be done by most physicians in general practice. At least in one study (9) it was shown that the second treatment may not be useful in behavior therapy, whereas it is useful in pharmacotherapy. This emphasized the fact that both forms of obesity treatment are effective provided that they are used properly.

Attitudes of patients toward any treatment of obesity must be considered in designing the treatment strategy in order to achieve maximal therapeutic effect. In the case of pharmacotherapy, drug compliance is very critical for the outcome of therapy. The combination as discussed in this study was well accepted.

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