

A Controlled Clinical Comparison of Benzphetamine and D-Amphetamine in the Management of Obesity

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BENZPHETAMINE (Didrex[®]) is a new anorexic drug which, it is hoped, will serve as a useful adjuvant in the management of obese patients. In a clinical study utilizing the double blind technic, we previously reported the clear statistically significant superiority of benzphetamine over placebo medication in the weight loss achieved by obese outpatients receiving these medicaments for a period of twenty weeks.¹ These results have been amply confirmed in subsequent publications by other clinical investigators.²⁻⁵ The purpose of the present report is to present the results of a follow-up study comparing the efficacy of benzphetamine and d-amphetamine in promoting weight loss in another group of obese outpatients for a period of twenty weeks. The present study also employed the double blind method.

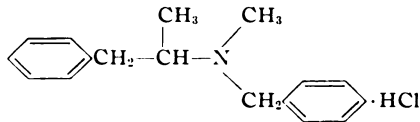
It was synthesized in the laboratories of The Upjohn Company. The pertinent laboratory data concerning the animal pharmacology and the human pharmacology of this compound were presented in detail in our previous publication.¹

The patients who participated in this study attended the obesity clinic at the Cedars of Lebanon Hospital, Los Angeles. Details concerning them are shown in Table 1. It can be seen that the makeup of the patients in both drug-treated groups was about the same. All the patients were under our care. They were subjected to the same weight reduction program with respect to diet, frequency of visits to the clinic and method in which the drugs were administered. The only major variables consisted of the drug dispensed, benzphetamine or d-amphetamine, and the supervising physician (either B. S. or L. W.). A 1,000 calorie, high protein diet was prescribed for each patient. The diet contained 100 gm. of carbohydrate, 84 gm. of protein, and 30 gm. of fat.

The study was performed by the double blind technic using the coded tablets No. 68 and No. 69, which were identical in appearance. Alternate, unselected patients were assigned first to one physician and then to the other. Alternate patients assigned to each doctor were then given the No. 68 and No. 69 tablets in turn. The patients were told to take one of these tablets fifteen minutes before each meal. In the event that weight loss was unsatisfactory, the dose was increased to two tablets before each meal. All in all, twenty patients were started on No. 68 tablets and nineteen on those labeled No. 69. Each patient was seen weekly for four weeks and then once every two weeks for a maximum of twenty weeks. Each patient continued either on the No. 68 tablet or the No. 69 tablet from the beginning to the end of the investigation. At the conclusion of this study, we were informed that the No. 68 tablets were benzphetamine and contained 40 mg. of drug per tablet, and that the No. 69

MATERIALS AND METHODS

Benzphetamine or (+) N-benzyl-N,a-dimethylphenethylamine hydrochloride has the following structural formula (dextro form):



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TABLE I
Patients Studied

Medication	No. of Patients	Mean Age (yr.)	Sex	Mean Weight (lb.)	Mean Overweight (%)
Benzphetamine.....	20	54	All F	188	53
d-Amphetamine.....	19	53	18 F, 1 M	190	56

tablets were d-amphetamine and contained 5 mg. of drug per tablet.

The degree of weight loss was expressed as the average pounds lost per patient, the average pounds lost per patient per week and the average performance index per patient. The performance index (P.I.) of a patient, according to the formula of Jolliffe and Alpert,⁶ is the actual weight loss over the predicted or hoped-for weight loss times 100. A perfect performance index is 100 per cent, and values less than 100 per cent indicate the approximate degree of the patient's adherence to the dietary program. Use of the performance index eliminates several possible variables by permitting comparison between persons of different sexes, ages, occupations, activities, weights and degrees of obesity.

RESULTS

The results of the study in terms of weight loss have been summarized in Tables II, III and IV. Table II shows the over-all weight loss for the entire duration of the study expressed as total pounds lost, pounds lost per week and total performance index. It is apparent from inspection of this table that there was no difference in the weight loss achieved by patients receiving benzphetamine or d-amphetamine. The slightly greater total weight loss of the patients receiving benzphetamine (15.78 pounds) compared with that of the patients receiving d-amphetamine (13.57 pounds) was not statistically significant ($t=0.7$). The mean weight loss per week of the patients in both drug groups is comparable to that reported in the previous literature for d-amphetamine and other amphetamine drugs. Furthermore, this weight loss significantly exceeds the weight loss exhibited by groups receiving placebos in two previous double blind studies conducted by us in the same clinic, with the same methodologic format, and with patients of similar composition in terms of age,

TABLE II
Double Blind Study Results in Patients Followed Up Eight Weeks or Longer

Medication	No. of Patients	Weeks Observed	Total Pounds Lost	Pounds Lost Per Week	Total Performance Index (%)
Benzphetamine.....	19	16	15.78 ± 2.91*	0.98 ± 0.14	36 ± 5.29
d-Amphetamine.....	17	15	13.57 ± 1.42	1.00 ± 0.12	37 ± 4.16

* Mean and standard error of the mean.

TABLE III
Performance Index at Four-Week Intervals

Medication	Four-Week Periods				
	1	2	3	4	5
Benzphetamine.....	66 ± 7.87* (20)	32 ± 5.11 (19)	25 ± 8.52 (16)	19 ± 6.89 (14)	17 ± 7.53 (9)
d-Amphetamine.....	52 ± 6.99 (19)	34 ± 4.52 (17)	21 ± 4.61 (12)	20 ± 9.90 (11)	9 ± 8.69 (8)

NOTE: Figures in parentheses indicate the number of patients.

* Mean (%) and standard error of the mean.

TABLE IV
Pounds Lost Per Week at Four-Week Intervals

Medication	Four-Week Period				
	1	2	3	4	5
Benzphetamine.	1.84 ± 0.23* (20)	0.86 ± 0.11 (19)	0.70 ± 0.24 (16)	0.49 ± 0.20 (14)	0.53 ± 0.23 (9)
d-Amphetamine.	1.53 ± 0.16 (19)	0.93 ± 0.16 (17)	0.56 ± 0.14 (12)	0.54 ± 0.24 (11)	0.29 ± 0.25 (8)

NOTE: Figures in parentheses represent the number of patients.

* Mean (lb.) and standard error of the mean.

TABLE V
Similarity of Benzphetamine Results in Two Separate Double Blind Studies

Benzphetamine Study	Total Pounds Lost	Pounds Lost Per Week	Total Performance Index (%)	Pounds Lost Per Week At Four-Week Intervals				
				1	2	3	4	5
First study.	16.01	0.90	32	1.60	0.83	0.73	0.78	0.43
Second study.	15.78	0.98	36	1.84	0.86	0.70	0.49	0.53

sex and percentage overweight.^{1,7} The weight loss in the groups receiving placebos was 0.28 pound per week¹ and 0.58 pound per week,⁷ respectively.

Tables III and IV show the weight loss at four-week intervals. Again, it can be seen that there was no difference in the weight loss achieved by the patients treated with benzphetamine or d-amphetamine. The somewhat greater weight loss exhibited by those receiving benzphetamine during the first and fifth four-week periods was not statistically significant. The weight loss for patients in both drug groups was greatest during the first four weeks of the study. In the ensuing sixteen weeks the patients receiving both drugs maintained a persistent significant weight loss except for those receiving d-amphetamine in the fifth four-week period, at which time the weight loss of this group was negligible. This effect of time on the rate of weight loss is similar to results previously published by us in two previous double blind studies of this type.^{1,7}

Table V shows the results of weight loss achieved by patients treated with benzphetamine in two different double blind studies con-

ducted approximately one year apart. The first study, previously reported by us, was a double blind study comparing patients treated with benzphetamine with patients treated with placebos.¹ These patients received doses of benzphetamine ranging from 25 to 50 mg. three times daily. The present study was conducted in the same manner except that patients receiving benzphetamine were compared with those receiving d-amphetamine. The dose of benzphetamine used in this study varied from 40 to 80 mg. three times daily. Inspection of the table reveals that the weight loss achieved by patients treated with benzphetamine in both studies was practically identical. The small differences between the two studies in the first and fourth four-week periods are not statistically significant. The data contained in this table illustrate two points. First, no further improvement in weight loss was induced by employing doses of benzphetamine greater than 25 to 50 mg. three times daily. Second, these data attest to the reproducibility of the findings achieved by the methodology employed in these two studies.

Table VI lists the side effects reported. No



TABLE VI
Side Effects Reported During This Study

Symptoms	Benzpheta- mine	d-Ampheta- mine
Gastrointestinal symp- toms.....	5	5
Dizziness.....	4	2
Constipation.....	2	3
Nervousness and poor sleep.....	5	6
Pruritus.....	1	1
Dryness or soreness of mouth.....	3	3
Chest pain.....	1	1
Headache.....	1	4
Malaise.....	1	2
Fatigue.....	1	5
Poor appetite control...	1	3

attempt was made to grade the severity of these side effects, since they were basically subjective in nature. These side effects were culled from complaints made by the patients at any time during the tenure of the twenty-week study. The side effects exhibited by the patients receiving benzphetamine and d-amphetamine were generally similar, with the following exceptions. The patients receiving benzphetamine complained of dizziness a little more frequently than those receiving the other drugs. On the other hand, the patients receiving d-amphetamine complained more of headache, malaise and fatigue.

COMMENTS

In this double blind study, the weight loss achieved by patients treated with benzphetamine and d-amphetamine was identical. The average weight loss of 1 pound per week over a fifteen- to sixteen-week period, achieved by the patients in both drug groups, compares favorably with rates of loss recorded in the literature for other anorexic agents. Studies on the efficacy of various amphetamine drugs have generally indicated average weight losses varying from 1 to 2 pounds per week over varying periods of time. In terms of potency, this study would indicate that 40 to 80 mg. of benzphetamine taken three times daily is equivalent to a dose of 5 to 10 mg. of d-amphetamine taken three times daily. If the results

of a previous double blind study performed by us comparing benzphetamine with placebos (Table v) can be interpolated here, the statement can then be made that 25 to 50 mg. of benzphetamine is equivalent to 5 to 10 mg. of d-amphetamine in potency. In this connection, data published by Oster and Medlar,² Schapiro and Bográn³ and Rhoades suggest that doses of benzphetamine of 50 to 100 mg. daily may be as effective as higher doses of this drug, 150 mg. daily. However, these observations at the present time must be considered suggestive since they are not statistically definitive.

At this writing, there is only one other published study in which the relative anorexic potency of benzphetamine and d-amphetamine were compared. This is the study of Poindexter⁴ who actually carried out a four-way double blind study comparing benzphetamine, phenmetrazine, d-amphetamine and placebos. He found that benzphetamine was superior to d-amphetamine in terms of weight loss, which was statistically significant. Since Poindexter's methodology was so much more complex and in many respects different than the procedure employed by us in this study, it was impossible directly to compare his findings with ours other than to note his conclusion.

The incidence and nature of side effects reported for the two drugs tested in this study were about the same. It was of interest to compare this with the side effects previously reported by us of a group of patients receiving placebos consisting of the same number of patients and of very similar composition in terms of age and weight. In a group of twenty such patients, five complained of nervousness, two, respectively, of palpitations, dizziness, dryness of the mouth and nausea, and three, respectively, of malaise and poor sleep. However, twelve of these patients complained of poor appetite control by the placebo drug. It would appear that the side effects of the patients receiving placebo are roughly comparable to those reported by the patients receiving benzphetamine and d-amphetamine in this study. There are two alternative explanations for these findings: (1) either benzphetamine and d-amphetamine did not give some patients a



better sense of well-being than did the placebo tablets, although they lost more weight and did not complain as much about hunger; or (2) many of the so-called side effects of anorexic agents are in reality symptoms of obese patients trying to stay on a low calorie diet. In this last respect, the side effects reported in this study bear a striking resemblance to those reported by Keys et al.⁸ in their classic controlled studies on human semi-starvation, which they have termed "semi-starvation neurosis." However, it should be emphasized that a definitive evaluation of subjective complaints such as reported here as side effects would require a more elaborate methodologic approach than was employed in this study. In this connection, it should be mentioned that in other studies by Schapiro and Bográn,³ Stough,⁵ Oster and Medlar² and Reiser et al.,⁹ it was found that side effects in patients treated with benzphetamine (particularly those of central nervous system stimulation) could be minimized by either tailoring the dose of the drug to the individual patient or by using smaller daily doses. Satisfactory weight loss without stimulation could be achieved in many patients with daily doses of benzphetamine of less than 100 mg.

Finally, if both drugs tested in this study, benzphetamine and d-amphetamine, were found to be equipotent in anorexigenic activity, and not significantly different in side effects, is there any clinical advantage in introducing another amphetamine drug for the treatment of obesity? The answer is yes. This positive assertion is based upon careful observation of the response of obese private patients to various amphetamine drugs over a period of several years. No one amphetamine drug is effective in *all* patients. No one drug is free of disturbing side effects in *all* patients. No single available amphetamine compound universally produces a significant anorexic effect with an accompanying sense of well-being in all patients. Some patients respond best to one drug, some to another. The amphetamine drug of choice must be tailored to the individual patient. In view of these practical observations of the *individual* obese patient, it is our conclusion that the more effective anorexigenic agents available, the larger

and more potent is the therapeutic armamentarium available to the supervising physician.

SUMMARY

A double blind study was performed comparing the efficacy of benzphetamine (Didrex) and d-amphetamine in the management of obese outpatients. It was found that both drugs were equally effective in inducing weight loss, which averaged 1 pound per week over a fifteen- to sixteen-week period for patients treated by each drug. It was found that 40 to 80 mg. benzphetamine was equivalent in anorexigenic potency to 5 to 10 mg. of d-amphetamine. Side effects registered for patients in both drug groups were similar in nature and frequency. Comparison with side effects noted in patients receiving placebos in previous studies suggested that some of the side effects were in reality the symptoms of obese patients undergoing semi-starvation on low calorie diets, rather than true effects of the drugs in question. In this and other studies, benzphetamine has been demonstrated to possess significant anorexigenic activity, and therefore is a useful aid in the management of obesity.

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