

EFFICACY OF LONG-TERM OBESITY'S TREATMENT WITH DIETHYLPROPION

GIORELLI, PAULO; RIBAS-FILHO, DURVAL; GIORELLI, SOCORRO; GIORELLI, GUILHERME

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ABSTRACT

Objective: To evaluate the efficacy and safety of long-term continuing treatment (24 months) of Diethylpropion (DEP) for weight loss in obese subjects.

Research Methods and Procedures: A large, multicenter, randomized, placebo-controlled, dose-ranging trial in 3688 subjects demonstrated that DEP plus individualized nutritional intervention causes a dose-dependent decrease in body weight. The long-term treatment (24 months) producing significantly greater weight loss than placebo at all doses, at month 24, weight loss for completers ranged from 2.3% in placebo-treated patients versus 25%, 33%, 52.3% and 52.5% in the 60, 100, 120 and 140 mg/d DEP groups, respectively. An individualized diet that was 600kcal/d less than maintenance needs was calculated and presented to each subject. All participants received the same lifestyle program. **Results:** Mean percent weight loss from baseline to month 24 was 2.3% in placebo-treated patients versus 25%, 33%, 52.3% and 52.5% in the 60, 100, 120 and 140 mg/d DEP groups, respectively. Greater percentages of DEP-treated patients lost at least 10% or 15% of body weight compared with placebo. The most frequent adverse events including dry mouth, constipation, insomnia, dizziness, tachycardia and palpitation. Most events were dose-related, occurred early in treatment, and usually resolved spontaneously; only 33% receiving DEP withdrew due to adverse events compared with 11% on placebo. **Discussion:** A 24 months randomized, placebo-controlled, dose-ranging trial of continuing Diethylpropion's therapy for weight loss in obesity. This prospective, multi-center study show clearly the efficacy of DEP for long-term treatment (24 months) producing significantly greater weight loss than placebo at all doses. This study sustain the use of weight management

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noradrenergic medications for long-term use (2 years or more) because of perceived benefit, comfort, and the absence of significant side effects. There has been no evidence of the development of tolerance, addiction, or misuse with minor adverse events related to the medication. The beneficial effects of the medication have not diminished with time.

Key words: obesity pharmacotherapy, long-term obesity's treatment, long-term obesity's treatment with diethylpropion

INTRODUCTION

The prevalence of obesity has been rising steadily throughout the world for more than 15 years (1, 3). The rise in obesity will undoubtedly be accompanied by increases in related disorders such as diabetes, hypertension, gall bladder disease and heart diseases. The associated health care costs will be High (4, 5).

Low calorie diet and physical activity remain the cornerstones of therapy for obesity, although results have been disappointing (1, 2 and 6). Obese patients who are able to lose weight by eating better and exercising generally regain the lost weight over time (1, 2 and 6). The difficulty in maintaining long-term weight loss through behavior modifications has led to an increasing interest in other avenues of treatment, particularly pharmacotherapy.

Diethylpropion (DEP) is catecholaminergic drug used since 1960, approved for Healthy authorities in Brazil.

To evaluate the efficacy and safety of DEP in treatment of obesity, we conducted one controlled clinical trial in obese subjects. We report here the results of this 24 months, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trial in obese subjects.

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Research Methods and Procedures

The clinical trial was limited to obese subjects who were between 18 and 60 years of age with a BMI of ≥ 30 to $< 50 \text{ kg/m}^2$ or ≥ 27 to $< 50 \text{ kg/m}^2$. Patients on anti-hypertensive or lipid-lowering medications were permitted to enroll only if their dose had been stable before beginning the study. They were not permitted to change dose during the study. Among those excluded from the trial were patients with recent weight change and those with diabetes, uncontrolled hypertension, liver disease, renal dysfunction, or psychiatric disease. Female subjects of child bearing potential were required to use an approved form of contraception and were tested for pregnancy at screening and monthly throughout the study.

The participants in this trial were recruited by two centers in Brazil: Trio de Janeiro, Rio de Janeiro State and Catanduva, São Paulo State. The study was carried out from July 2003 to July 2005. It was conducted in accordance with the Declaration of Helsinki (15) and Good Clinical Practice and approved by Institutional Review Boards at all sites. Informed consent was obtained from each patient before study-related procedures were initiated

TRIAL DESIGN

During an initial one week screening period, volunteers were assessed with a complete medical examination, including history and physical examination, blood tests, and electrocardiograms. Eligible subjects were randomized to receive placebo or 60, 100, 120 or 140 mg daily of DEP.

A 7 week drug titration schedule was used. An initial dose of 20mg once daily was administered in week 1 and raised to 10 mg twice a day at week 2. This twice daily regimen was then titrated upward in weekly increments of 20 mg/day (10 mg twice daily) until the target dosage was reached. The time needed to reach the target dosage of DEP was 3, 5, 6 or 7 weeks for the 60, 100, 120 and 140 mg/d dose groups,

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respectively. Subjects, investigators, and those administering the treatments were blinded to group assignments. No access to unblinding information was available to those gathering or processing patient data until all study procedures were completed, all database changes were finalized, and the database was released.

If intolerable side effects occurred at any dose including placebo, the clinical site could reduce by one level and continue treatment in a blinded fashion at this reduced dose for the remainder of the study (placebo group was reduced to placebo). Only one dose reduction was allowed. The number of subjects who were those reduced each treatment group is show in table 1. Subjects were withdrawn from the study if intolerable adverse events continued. All subjects participated in a standardized program which focuses on lifestyle and self-management in areas related to weight loss and obesity.

An individualized diet that was 600kcal/d less than maintenance needs was calculated and presented to each subject.

At the end of maintenance, subjects were tapered off the medication by reducing the dose by 50% per month for 2 months. A follow-up evaluation was performed 2 months after treatment was stopped.

ASSESSMENTS

Body weight was measured at each visit using a standard calibrate scale. Blood pressure was measured at each visit and recorded as the mean of three sitting measurements taken after a 5-minute rest using a standard sphygmomanometer. Venous blood samples were obtained from subjects after they had fasted over night at screening, baseline and monthly visits thereafter. All blood samples were analyzed in the same laboratory for standard electrolytes, blood urea nitrogen, creatinine, liver

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biochemistries, lipids, and complete blood count. Electrocardiograms were obtained at baseline and month 24. Adverse events were determined at each visit.

STATISTICAL ANALYSIS METHODS

The sample size was determined based on the aim of achieving 90% power to detect a 4% difference between the mean weight loss in the placebo and active doses. Because the primary objective was the comparison of each active dose to placebo, statistical testing of all possible combinations among the active doses was not part of the pre-planned set of analyses for which multiple comparison adjustments were made. This enabled the attainment of the maximum degree of statistical power for the comparisons of primary interest, which were the comparisons of each active dose to placebo.

Efficacy data were assessed in the intent-to-treat (ITT) population, defined as all subjects who were randomized, received at least one dose of study medication, and completed at least one efficacy measurement while on treatment. Analyses involving changes from baseline to month 24 used the last-observation-carried-forward (LOCF) approach, i.e. if a subject had no data at month 24, then the last recorded observation before that visit was used. Efficacy analyses were also performed on the population of subjects who completed the study (completers), defined as all randomized subjects who had a baseline assessment and a month 24 maintenance assessment with at least 700 days on therapy.

The primary efficacy variable-percent change from baseline body weight at month 24 was analyzed using an analysis of covariance model with treatment and center as factors in the model. Sex and baseline body weight were included as covariates. To evaluate the weight-loss effect of DEP at different dose levels compared with placebo and to adjust for multiple comparisons for the four active doses, the step-

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down multiple testing frameworks for comparing treatments with a control in unbalanced layouts suggested by Dunnett and Tarnhane (16) was used. Implementation of this methodology produces p values that have been appropriately adjusted upward, so that for convenience, we can compare them to the usual value of 0.05. The method, therefore, allows the assessment of an adjusted p value for each comparison at the 0.05 significance level while maintaining the family-wise false positive rate of 0.05. For the primary efficacy measure, the two-sided significance level, α , was 0.05.

An important secondary efficacy assessment compared treatment groups with respect to the percentage of subjects who lost at least 5% or 10% of body weight, stratified by sex. Other secondary endpoints were the change from baseline to month 24 in kilograms of body weight, BMI, anthropometric measures, lipid profile, fasting plasma glucose, hemoglobin A1C (Hb A1C) fasting insulin, uric acid, and systolic (SBP) and diastolic blood pressure (DBP). These variables were analyzed in a manner similar to that of the primary efficacy endpoint, except that nominal significance levels were provided for the secondary endpoints. Gender and the respective baseline values were included as covariates in each analysis of covariance model.

Safety data included treatment-emergent adverse events, cognitive test scores, laboratory analyzes values, vital sign measurements, and electrocardiogram data reported during the trial. The population used for safety evaluation was defined as all randomized subjects who received at least one dose of study drug and provided at least one post baseline safety measurement. The Kaplan-Meier method (17) was used to examine the relationship between time on study medication and the occurrence of selected treatment-emergent adverse events. Analyses of the safety did not rely on statistical significance level testing, because the study was not powered for safety endpoints, and the comparisons of interest were not prespecified. All pertinent safety data are presented descriptively irrespective of statistical significance or lack thereof.

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RESULTS

A total of 3866 participants were randomized. Of these, 3800 patients had one safety measurement and were included in the safety population; 3760 completed one efficacy measurement and were included in the efficacy analysis. A total of 2600 subjects (67%) completed the trial. Baseline characteristics were balanced across dose groups, as shown in table 1. The average age was $44,9 \pm 11.4$ years. More than 80% of the participants were pre-menopausal women. Only 2% of the subjects were more than 58 years old. Mean weight was 103.7 ± 17.7 kg, and mean BMI was 37.4 ± 5.2 kg/m². Ten percent of patients were hypertensive (defined as baseline SBP > 140 mm Hg and/or DBP >90 mm Hg); 17% of placebo-treated subjects and 13% of DEP-treated subjects were receiving antihypertensive medication at baseline. Five percent of placebo treated and 6% of DEP-treated subjects were taking lipid lowering medications at baseline.

CHANGE IN BODY WEIGHT

DEP produced significantly greater weight loss than placebo at all doses ($p < 0.05$) after month 4. The weight loss was almost the same with the two higher doses, which produced more weight loss than the lower doses. Weight loss continued throughout the trial and did not plateau at 24 months. At 24 months, weight loss in the ITT-LOCF population was 2.6% for placebo and 5.0%, 4.8%, 6.3% and 6.5%, respectively, for groups treated with 60, 100, 120 and 140 mg/d DEP (corresponding to mean decreases of 2.8 kg for placebo and of 5.0, 5.2, 6.4 and 6.6 kg, respectively, for the 60, 100, 120, and 140 mg/d DEP groups). Among the completers, those receiving placebo experience 36,6% weight loss compared with losses of 5,8%, 6,5%, 8,2% and 8,5%, respectively, for those receiving 60, 100, 120 and 140 mg/d DEP (corresponding

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to mean losses of 3,9kg for placebo and 6.0, 6.8, 8.3 and 8.9 kg respectively for the 60, 100, 120 and 140 mg/d DEP groups.

Notable weight loss among the completers was also observed by month 4 and continued to decrease through the 24 month period, BMI decreased more in DEP-treated patients than in the placebo group, with the two higher doses producing similar decreases that were greater than those observed with the two lower doses, as evaluated either in the ITT population (0.5kg/m² for placebo and 1.5, 1.4, 1.8 and 1.9 kg/m², respectively, for the 60, 100, 120 and 140mg/d DEP groups) or in the population of completers (1.3 kg/m² for placebo and 2.2, 2.4, 3.0 and 3.2 kg/m², respectively, for the 60, 100, 120 and 140mg/d DEP groups).

For both populations and at all doses of DEP, the percentage of subjects who achieved at least a 5% weight loss was significantly greater in the DEP-treated groups than in the placebo-treated group. This was also true in those who achieved at least 10% weight loss for the three highest DEP doses 100, 120 and 140 mg/d in the ITT population and for the two highest doses 120 and 140 mg/d in the completer population. The percentage achieving 5% and 10% weight loss increased significantly from placebo to 60 mg/d and 100 mg/d; it was maximal at 120 mg/d. The highest dose (140 mg/d) was associated with a smaller percentage achieving 5% and 10% than with 120 mg/d.

CARDIOVASCULAR AND METABOLIC RISK FACTORS

Although most patients had normal BP measurements at baseline, significant decreases were observed in SBP for each of the four DEP treatment groups (4.5, 5.8, 7.1 and 7.5 mm Hg for the 60, 100, 120 and 140 mg/d groups respectively, vs 1.2 mmHg for placebo; p<0,05, ITT-LOCF).

As expected, in those subjects who lost more than 5% or 10% of body weight, there were greater reductions in BP and modest changes in total cholesterol, low-density lipoproteins (LDLs), and triglycerides.

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TOLERABILITY, SAFETY DATA AND ADVERSE EVENTS

Table 2 shows adverse events that occurred in more than 5% of DEP treated subjects across the four treatment groups. Most of these events involved the central (CNS) or peripheral nervous systems and were mild to moderate in severity. A grouping of related events is characterized in Table 2 as "CNS-related," defined as any event occurring within the central or peripheral nervous body systems or psychiatric body system, as well as fatigue (as defined by the World Health Organization Adverse Reaction Terminology adverse event coding dictionary).

Adverse events were the cause of discontinuation in 11 % of the placebo-treated patients and in 21% of the DEP treated patients ($p < 0.05$). The most common side effects leading to discontinuation: insomnia, dizziness, difficulty with concentration or attention, and mood problems (leading to discontinuation in 6%, 4%, 3%, and 3% of all DEP-treated patients, respectively) generally showed a pattern of increasing incidence with increasing dose. Serious adverse events occurred in 12 (4%) of DEP - treated and in 2 (3%) of placebo-treated subjects. Three serious adverse events in the DEP group were considered to be possibly related to drug therapy: 1) renal calculus (patient continued in study); 2) increased hepatic enzymes of unknown etiology (patient withdrew from study); and 3) injury secondary to motor vehicle accident (patient withdrew from study). All three of these possibly related serious adverse events resolved.

DISCUSSION

This is the first Brazilian long-term (24 months) prospective randomized clinical trial of DEP in obese patients. Most were premenopausal women who had few features of the metabolic syndrome. In this trial, DEP produced significantly greater

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weight loss than placebo at all doses. The two lower doses produced similar weight loss, which was less than that produced by the two higher doses. This was evident in both the completers and ITT-LOCF analysis.. All DEP groups experienced significantly greater decreases in body weight by month 4 than the behavioral modification group that also received placebo drug. The PATHWAYS TO CHANGE behavioral intervention has not previously been used in drug clinical trials; therefore, there are no data evaluating its efficacy in patients who received behavioral intervention without placebo.

Body weight continued to decline throughout the 24 month trial at all doses. The continuing decline in body weight in DEP-treated subjects at 24 months suggests that the clinical effect will take longer than 24 months achieve.

This observation is consistent with the analysis of the DEP clinical database, has been no evidence of the development of tolerance, addiction, or misuse and no adverse events related to the medication. The beneficial effects of the medication have not diminished with time.

In a recent study, Professor Arthur Frank (28), described 25 years with no interrupt treatment with DEP with any evidence of tolerance, addiction, or misuse and no adverse events related to the medication.

Ongoing weight-loss beyond 6 months would be an important consideration, because studies with other weight loss drugs phentermine (20), dexfenfluramine (21), phentermine/fenfluramine (22), sibutramine (6,23), and orlistat (8,24,26) show that mean weight loss reaches a nadir by 6 months and that 75% of maximal weight loss is achieved by 3 months (27). Additional long-term prospective clinical trials in obese patients will be required to determine the time-to-nadir and the maximal weight loss produced by others catecholaminergic drugs.

A weight loss of 5% to 10% can bring considerable health benefits by improving or reversing obesity-related comorbidities and preventing the onset of new disease related to obesity (6,28). In this study, the number of subjects losing more than

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5% or 10% of their baseline body weight increased as the dose of DEP increased from 60 mg/d through the dose of 120 mg/d. For reasons that are unclear, there was no further increase in the percentage losing weight at the highest dose of 140 mg/d. In general, the percentage of patients treated with DEP who achieved a 5% or 10% weight loss was two to three times the percentage among those treated with placebo. This so-called "responders" analysis has been a useful tool in showing what fraction of patients may be expected to have a clinically significant response to a weight-loss medication when the physician uses the medication in a treatment setting.

Treatment with DEP was associated with a significant decrease in SBP and DBP, which is consistent with the effects observed for weight loss in non hypertensive subjects. In these data, a weight loss of 1 kg was associated with a 5 mm Hg reduction in both SBP and DBP. In contrast with its effect on BP, DEP therapy was not associated with significant changes in plasma lipids. In a meta-analysis of the effect of weight loss on blood lipids, a decrease in body weight of 1 kg predicted a decrease of -0.05 mM in total cholesterol, an increase of 0.007 mM in high-density lipoprotein-cholesterol (HDL-C), and a decrease of 0.015 mM in triglycerides (all $p \leq 0.05$). In three randomized clinical trials of 6-month duration (7), there was an association between loss of weight and decrease in total cholesterol, LDL-C, and triglycerides, and an increase in HDL-C. The lack of an effect of DEP on the lipid parameters in this trial may be because of the baseline values in our study subjects, which were tightly clustered within the normal range. A similar conclusion may be reached because of the lack of change in plasma glucose during treatment in this study of nondiabetic subjects. The effects of DEP on BP, lipids, and glucose may be best demonstrated in longer term studies in obese patients with hypertension, dyslipidemia, and type 2 diabetes. The most common side effects of therapy-central or peripheral nervous system events-were dose-related and predominantly mild to moderate in severity. DEP was better tolerated at the lower doses of 60 and 100 mg/d than at the higher doses. Adverse events were more frequently

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reported during the titration phase of the trial.

Certain cognitive adverse events were reported more frequently at higher DEP doses, including difficulty with memory, difficulty with concentration or attention and insomnia. Most of these events resolved spontaneously, often without dose reduction or drug discontinuation.

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TABLE 1: Baseline characteristics of study participants

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Table 1. Baseline characteristics of study participants

Characteristic	GIORELLI, PAULO; RIBAS-FILHO, DURVAL; GIORELLI, SOCORRO; GIORELLI, GUILHERME				
	Placebo (n = 738)	DEP 60 mg/d (n = 737)	DEP 100 mg/d (n = 738)	DEP 120 mg/d (n = 737)	DEP 140 mg/d (n = 738)
Age (yrs)	44.6 ± 11.1	45.1 ± 11.1	45.3 ± 11.7	44.3 ± 12.0	45.4 ± 11.2
Number randomized	738	737	738	737	738
Number completed	480	530	480	490	440
Number dose-reduced	50	70	90	140	200
Sex					
Male	78 (10.5%)	107 (14.5%)	98 (13.27%)	97 (13.16%)	68 (9.22%)
Female	660 (89.5%)	630 (85.5%)	640 (86.73%)	640 (86.84%)	670 (90.78%)
Race					
White	51 (68%)	60 (79%)	59 (79%)	61 (80%)	59 (76%)
Black	21 (28%)	13 (17%)	13 (17%)	14 (18%)	16(21%)
Other	3 (4%)	3 (4%)	3 (4%)	1 (1%)	3 (4%)
Weight (kg)	105.4 ± 16.7	103.1 ± 17.1	104.6 ± 16.1	101.0 ± 18.8	104.5 ± 19.5
BMI (kg/m ²)	38.0 ± 5.5	37.3 ± 4.9	37.6 ± 4.9	36.6 ± 5.5	37.4 ± 5.2
SBP (mm Hg)	121.2 ± 13.1	120.7 ± 12.2	121.6 ± 12.9	121.3 ± 12.4	121.3 ± 13.1
DBP (mm Hg)	79.8 ± 9.4	77.8 ± 7.3	78.9 ± 7.7	79.0 ± 8.7	77.7 ± 8.3
Total cholesterol (mM)	5.0 ± 0.9	5.2 ± 0.9	5.2 ± 0.9	5.2 ± 0.8	5.1 ± 0.9
LDL (mM)	3.0 ± 0.8	3.3 ± 0.8	3.2 ± 0.8	3.3 ± 0.7	3.1 ± 0.7
HDL (mM)	1.3 ± 0.3	1.2 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.4
Triglycerides (mM)	1.6 ± 0.9	1.6 ± 1.0	1.5 ± 0.8	1.6 ± 0.8	1.6 ± 0.8
Fasting glucose (mM)	5.5 ± 1.3	5.4 ± 0.6	5.3 ± 0.6	5.2 ± 0.5	5.3 ± 0.8
HbA _{1c} (%)	5.8 ± 0.8	5.7 ± 0.5	5.6 ± 0.5	5.6 ± 0.5	5.7 ± 0.5

EFFICACY OF LONG-TERM OBESITY'S TREATMENT WITH DIETHYLPROPION

GIORELLI, PAULO; RIBAS-FILHO, DURVAL; GIORELLI, SOCORRO; GIORELLI, GUILHERME

TABLE 2: Adverse Effects of Diethylpropion Therapy

Adverse Effect	Placebo Subjects (%)	Diethylpropion Subjects (%)
Dry mouth	4.2	27.2
Constipation	6.0	11.5
Insomnia	4.5	6.7
Dizziness	3.4	4.0
Hypertension	0.9	1.1
Tachycardia	0.6	2.6
Palpitation	0.8	2.0