

## ORIGINAL ARTICLE

# A randomized double-blind placebo-controlled study of the long-term efficacy and safety of diethylpropion in the treatment of obese subjects

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**Objective:** To evaluate the efficacy of diethylpropion on a long-term basis, with emphasis in cardiovascular and psychiatric safety aspects.

**Design:** Randomized, double-blind, placebo-controlled trial

**Measurements:** Following a 2-week screening period, 69 obese healthy adults received a hypocaloric diet and were randomized to diethylpropion 50 mg BID ( $n = 37$ ) or placebo ( $n = 32$ ) for 6 months. After this period, all participants received diethylpropion in an open-label extension for an additional 6 months. The primary outcome was percentage change in body weight. Electrocardiogram (ECG), echocardiography and clinical chemistry were performed at baseline and every 6 months. Psychiatric evaluation and application of Hamilton rating scales for depression and anxiety were also performed by experienced psychiatrists at baseline and every 3 months.

**Results:** After 6 months, the diethylpropion group lost an average of 9.8% (s.d. 6.9%) of initial body weight vs 3.2% (3.7%) in the placebo group ( $P < 0.0001$ ). From baseline to month 12, the mean weight loss produced by diethylpropion was 10.6% (8.3%). Participants in the placebo group who were switched to diethylpropion after 6 months lost an average of 7.0% (7.7%) of initial body weight. The difference between groups at month 12 was not significant ( $P = 0.07$ ). No differences in blood pressure, pulse rate, ECG and psychiatric evaluation were observed. Dry mouth and insomnia were the most frequent adverse events.

**Conclusion:** Diethylpropion plus diet produced sustained and clinically significant weight loss over 1 year. It seems to be safe in relation to cardiovascular and psychiatric aspects in a well-selected population.

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**Keywords:** diethylpropion; treatment; appetite-suppressant drugs; sympathomimetic

## Introduction

Obesity contributes greatly to morbidity and mortality and significantly increases the risk of chronic and potentially disabling conditions associated with overweight status such as diabetes, hypertension, dyslipidemia, coronary artery disease and ischemic stroke.<sup>1–3</sup> There are few options for the treatment of obesity, mainly for a long-standing use. At present, only two drugs are approved for the long-term treatment of overweight patients—sibutramine and orlistat.<sup>4,5</sup>

Appetite-suppressant drugs, by reducing overall hunger sensation, can help obese patients diminish weight.<sup>6</sup> Despite apparent differences in pharmacology and abuse potential, there is still a tendency to refer to all centrally acting sympathomimetic appetite suppressants as ‘amphetamine-like’ and to view them all with equal harm potential. Amphetamine induces marked central nervous system effects, reducing sleep and appetite, increasing blood pressure, while producing central nervous system stimulation, euphoria and diminished fatigue. The modifications in the chemical structure that characterizes the class of anorectics are of two types: side-chain modification and ring modification. Anorectics such as diethylpropion have side-chain modifications and retain some stimulant activity but on a reduced level.<sup>7</sup>

Diethylpropion is a phenylethylamine ring compound with minor sympathomimetic properties and with less stimulant effects than amphetamine. It has been approved

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for the treatment of obesity for 50 years, but in spite of this, it has not been adequately studied.<sup>8</sup> A recent meta-analysis that assessed the use of diethylpropion for weight loss in obese individuals identified 13 studies published between 1965 and 1983. The duration of treatment with diethylpropion varied from 6 to 52 weeks, but the preponderance of studies was less than 20 weeks.<sup>9</sup>

Few studies have evaluated the long-term use of diethylpropion.<sup>10–12</sup> Obesity is a lifelong condition and the great majority of individuals who lose weight will eventually regain it. A long-standing treatment can be justified to prevent weight regain but more data on the efficacy and safety of this drug are needed. The aim of this study was to evaluate the efficacy of diethylpropion on a long-term basis, with emphasis in cardiovascular and psychiatric safety aspects. To our knowledge, this is the only long-duration sympathomimetic appetite suppressant study that cautiously analyzed cardiovascular and psychiatric safety aspects.

## Methods

### Patients

This study was approved by the institutional review boards of the Hospital das Clínicas, University of São Paulo-Brazil, and was conducted at the Obesity and Metabolic Syndrome Group. Written informed consent was obtained from all participants before entry into the trial. A hundred and one patients, from both sexes aged 18 years or older, were recruited from waiting lists for treatment of obesity between May 2004 and November 2005 (Figure 1). Entry criteria included body mass index (calculated as weight in kilograms divided by the square of height in meters)  $\geq 30$  and  $\leq 45 \text{ kg m}^{-2}$ . Patients were excluded if they had a body weight fluctuation of more than 4 kg in the previous 3 months; made use of medications that alter body weight or appetite; presented clinically significant cardiac, renal, hepatic, neurological or endocrine disorders; were drug-treated or diagnosed with type 1 or type 2 diabetes; and were pregnant. Exclusion criteria related to psychiatric condition were a history or current case of severe anxiety, depressive disorder, bipolar disorder, psychotic disorders and substance abuse disorders, except tobacco use. Patients also were excluded if they had a score  $\geq 9$  at the Hamilton rating scales for depression and anxiety during screening phase or at any of the three following psychiatric evaluations (one interview every 12 weeks of treatment). Women with childbearing potential were required to use medically approved contraception.

### Study design

This study was a randomized, double-blind, placebo-controlled trial conducted for 6 months (phase 1), after which all participants received diethylpropion in an open-label extension for an additional 6 months (phase 2). Following a

2-week screening period, patients were instructed to follow a hypocaloric diet (30% of the total daily intake from fat, 15% from protein and the remainder from carbohydrate). The diet prescription was adjusted to each patient's basal metabolic rate estimated by the Harris-Benedict equation and self-reported physical activity at screening to promote a deficit of 600 kcal per day in relation to the calculated daily intake to maintain body weight. Patients also were instructed to increase their level of physical activity throughout the study. All the patients had been counseled to carry through at least 150 min of physical activity per week.

Patients were randomly allocated to placebo or 50 mg Twice a day (BID) of diethylpropion sustained-release tablet. After 6 months, all participants received diethylpropion (50 mg BID) in an open-label extension for an additional 6 months period. The sequence of randomization was computer generated by Medley Pharmaceutical Medley Pharmaceutical, São Paulo, Brazil for a total of 100 patients. Eligible participants were allocated following a numeric sequence. Medley Pharmaceutical (São Paulo, Brazil) manufactured and provided both placebo and diethylpropion for the study. Placebo capsules looked exactly like diethylpropion capsules and were dispensed in the same way. Medication compliance, defined as consumption of at least 80% of capsules, was assessed by capsule counting at each specified visit.

The patients were instructed not to start other concomitant weight loss medications or other weight loss treatments during the study. They complied with this recommendation.

### Assessments

Initial screening included a medical history, physical examination, electrocardiogram (ECG), echocardiography, clinical chemistry, thyroid function and hematology. Psychiatric evaluation and application of Hamilton rating scales for depression and anxiety were also performed during the screening phase by experienced psychiatrists. Body weight was measured using a calibrated digital scale at screening and after 2 weeks and then every 4 weeks. Waist circumference was measured using a spring-loaded measuring tape midway between the lower rib and iliac crest and followed the same measurement schedule as body weight. Systolic and diastolic blood pressure and pulse rate were obtained in all visits after the patient stayed still for at least 5 min. Serum glucose, insulin and lipids were assayed according to standard procedures at baseline, month 6 and at the end of the study. Insulin resistance analysis was carried out through Homeostasis Model Assessment (Homeostasis Model Assessment of Insulin Resistance).<sup>13</sup> Concomitant medications, such as antihypertensive and lipid-lowering treatment, were documented and the doses were maintained stable throughout the trial.

### Safety evaluations

Each safety evaluation included a physical examination with the collection of vital signs and the recording of adverse

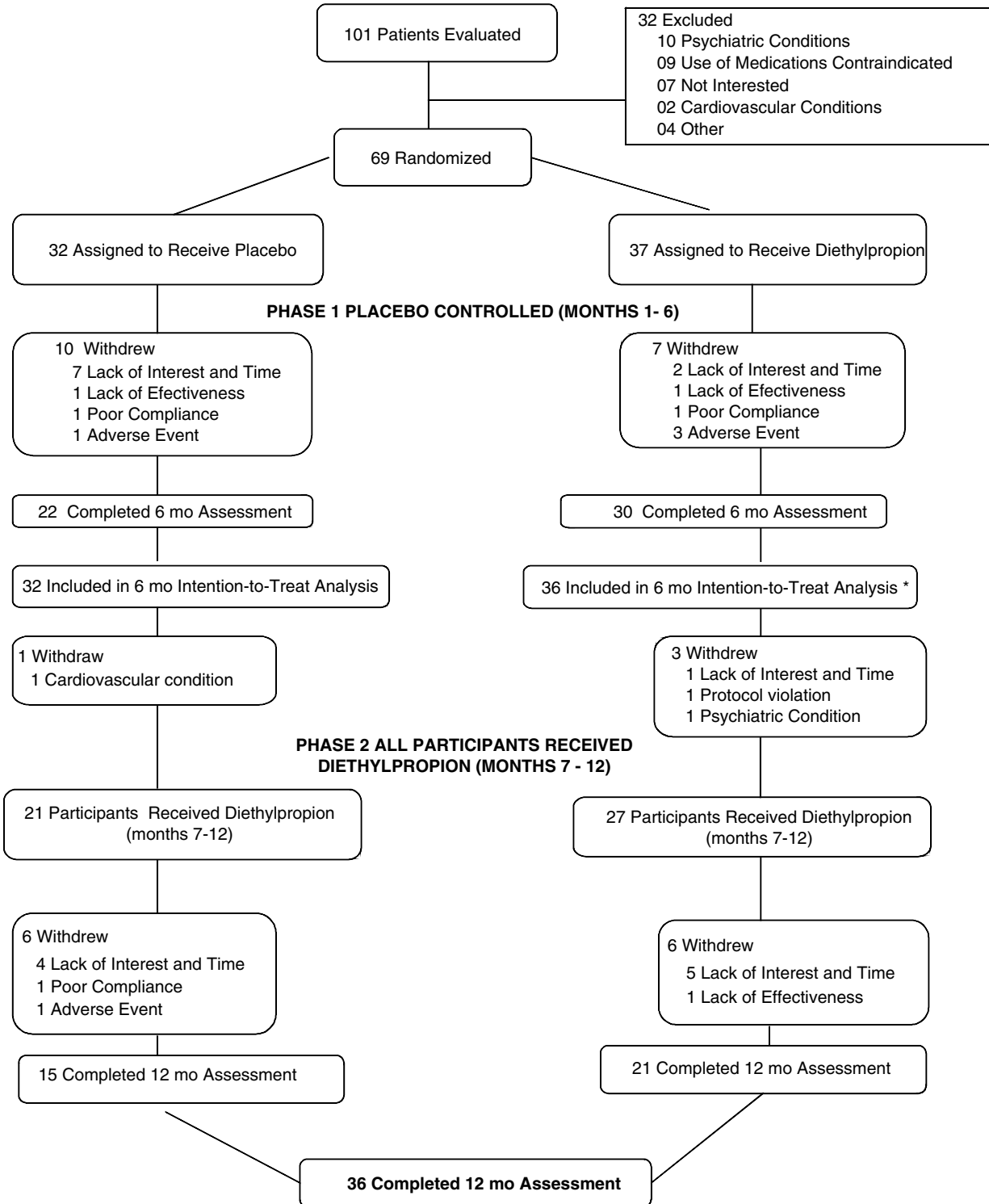


Figure 1 Flow of participants throughout the trial.

events. Psychiatric visit and Hamilton rating scales for depression and anxiety were assessed every 3 months. Hematology and serum chemistry were evaluated every 6 months. Electrocardiogram and echocardiography were performed every 6 months. Adverse events were assessed by active questions at each visit.

#### End points and measures of outcome

The primary study end point was change in absolute body weight in kilograms and percent change in weight from baseline to final assessment. In addition, we examined the number of participants in each group who achieved weight losses of 5% or greater and 10% or greater. Secondary outcome measures included heart rate, blood pressure, changes in waist circumference, fasting glucose and insulin levels, Homeostasis Model Assessment of Insulin Resistance, triglycerides, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol.

#### Statistical analysis

The sample size was estimated to provide 80% power to detect treatment differences in body weight with an  $\alpha$ -level of 0.05, assuming a dropout rate of 35%. Longitudinal changes were analyzed using repeated-measures analysis of variance.<sup>14</sup> In all efficacy analyses, the primary population of interest was the modified intention-to-treat population with the last observation carried forward, defined as all participants who received at least 1 dose of study medication and recorded at least 1 post-baseline. A Tukey–Kramer adjustment was used for the *post hoc* comparison of the groups at each time point.<sup>15</sup> Statistical end points included changes from baseline to each time point. Categorical measures were analyzed using  $\chi^2$  test or Fisher's exact test when appropriate.<sup>16</sup> Odds ratios and their 95% confidence intervals were calculated as appropriate. Student's unpaired *t*-test was used to compare quantitative variables between two independent groups. Paired *t*-test was used to compare quantitative variables between two paired groups. All statistical tests were two-sided and were considered to be significant at a *P*-value <0.05. All computations were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA).

## Results

A total of 101 patients were evaluated and 69 were randomized to double-blind treatment with placebo ( $n=32$ ) or diethylpropion 50 mg BID ( $n=37$ ). The disposition of patients over 1 year is shown in Figure 1. The characteristics of the study population at randomization were similar in both treatment groups (Table 1). Sixteen (nine in the diethylpropion group and seven in the placebo group) out of 69 randomized patients were using antihypertensives and only one patient (from the placebo group) was using lipid-lowering treatment in the baseline. The doses were maintained stable throughout the trial. Phase 1 was completed by 68.7% of patients ( $n=22$ ) in the placebo group and 81.0% ( $n=30$ ) in the diethylpropion group. A total of 48 patients who completed phase 1 continued on phase 2 open-label diethylpropion treatment. The completion rates for open-label phase in 6–12 months were 75.0%. One patient in the diethylpropion group took only one capsule, presented general discomfort and did not return to the hospital. She was not included for weight and metabolic assessment intention-to-treat (ITT) analysis, but she was included for adverse events analysis (Figure 1).

#### Body weight change

For the first 6 months during phase 1 (placebo controlled), participants in the diethylpropion group lost a mean (s.d.) of 9.3 kg (6.6 kg) or a 9.8% (6.9%) reduction in initial weight using intention-to-treat with last observation carried forward analysis (Figure 2 and Table 2). In contrast, patients treated with placebo lost 3.1 kg (3.6 kg) or a significantly smaller 3.2% (3.7%) reduction in weight ( $P<0.0001$ ). In phase 2 (open-label diethylpropion treatment), participants who were originally treated with placebo and were switched to diethylpropion from months 7 to 12 lost an additional 3.6 kg during this period. In contrast, participants originally treated with diethylpropion who continued medication lost an additional 0.8 kg during months 7–12. From baseline to month 12, participants treated throughout the study with diethylpropion lost a total of 10.1 kg (7.9 kg) or a 10.6% (8.3%) reduction in initial weight. Those participants in the placebo group who were switched at month 7 to

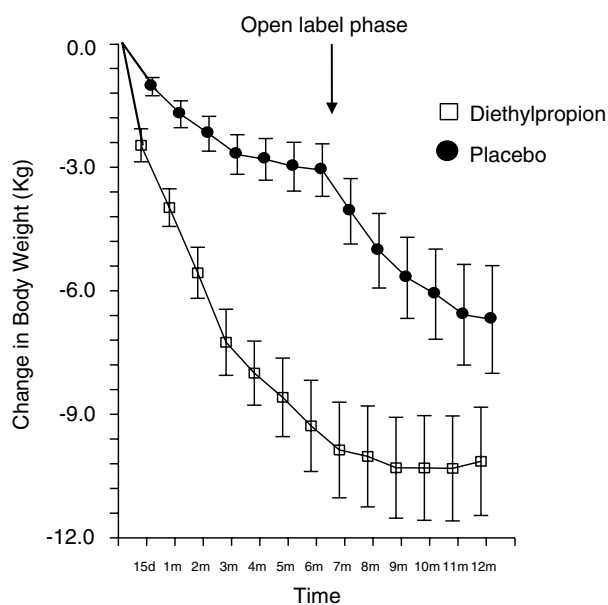
**Table 1** Patient characteristics at baseline according to treatment assignment

Characteristics	Placebo (n = 32)	Diethylpropion (n = 37)	P-value vs placebo
Sex, female (%)	28 (87.5)	35 (94.6)	0.40
Age, mean (s.d.), years	35.6 (10.4)	38.0 (10.8)	0.35
BMI, mean (s.d.), kg m <sup>-2</sup>	36.5 (3.7)	37.0 (3.6)	0.58
Weight, mean (s.d.), kg	96.3 (14.5)	95.5 (15.1)	0.84
Waist, mean (s.d.), cm	107.1 (8.2)	108.0 (9.5)	0.70
Height, mean (s.d.), cm	162.0 (7.4)	160.3 (7.4)	0.35
Systolic blood pressure, mean (s.d.), mm Hg	126.1 (9.7)	125.8 (12.0)	0.93
Diastolic blood pressure, mean (s.d.), mm Hg	71.4 (7.8)	73.0 (10.6)	0.48
Pulse rate, mean (s.d.), b.p.m.	77.9 (14.2)	82.2 (8.5)	0.12

diethylpropion lost a total of 6.7 kg (7.4 kg) or a 7.0% (7.7%) reduction in initial weight. The difference between groups at month 12 was not significant ( $P=0.07$ ). The percentage of patients achieving a 5% or greater weight loss at month 6 was 25.0% for patients receiving placebo and 67.6% for patients receiving diethylpropion ( $P=0.0005$ ). The percentage of patients achieving a 10% or greater weight loss was 3.13% for patients receiving placebo and 51.3% for patients receiving diethylpropion ( $P<0.0001$ ) (Figure 3). Compared with the patients receiving placebo, waist circumference decreased more in the patients receiving diethylpropion (Table 2).

### Cardiometabolic risk factor change

There were no significant differences between diethylpropion and placebo groups in the mean of cardiometabolic risk factors over time, except for triglyceride levels ( $P=0.007$ ).



**Figure 2** Change from baseline for body weight over 1 year. After 6 months, all participants received diethylpropion (open-label phase).

When we compared the changes of cardiometabolic factors in relation to baseline we found that levels of high-density lipoprotein cholesterol increased significantly in patients receiving either placebo or diethylpropion and levels of total cholesterol, low-density lipoprotein cholesterol and triglycerides decreased in patients receiving diethylpropion but did not in patients receiving placebo. Fasting glucose, insulin levels and insulin resistance estimated by the Homeostasis Model Assessment of Insulin Resistance decreased significantly in patients receiving diethylpropion but did not in patients receiving placebo (Table 3).

### Adverse events

Adverse events that occurred in more than 10% of the patients are shown in Table 4. The difference between the groups was statistically significant for dry mouth and insomnia only in the beginning of the treatment. After 3 months, no differences were observed between groups. Three patients withdrew due to adverse events in the diethylpropion group (two due to insomnia and one due to general discomfort) and one in placebo group (due to anxiety and depression)

### Cardiovascular safety

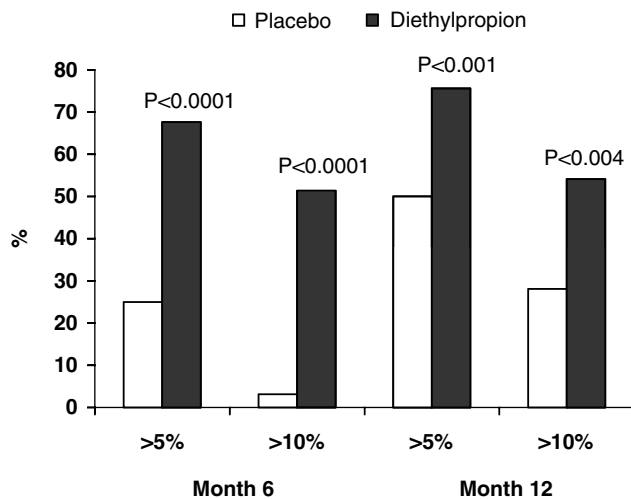
Mean systolic and diastolic blood pressure decreased during follow-up and were not different over time between the groups (Figure 4). Mean supine pulse rate for the diethylpropion and placebo treatment groups at baseline was 82.2 and 77.9 b.p.m., respectively. No statistically significant increases or decreases in mean postural pulse rate were found in either treatment group during the study. There was no clinically relevant abnormal finding or worsening of a baseline finding on ECG performed at baseline, month 6 and month 12 in both groups. Echocardiogram was performed at baseline and at months 6 and 12 of the study. One patient had an increase in pulmonary artery pressure (43 mm Hg) estimated by the echocardiogram realized at the end of the double-blind phase (month 6), and this change was not seen in the baseline examination. The study code was broken and she was in placebo group. There were no other significant echocardiograph alterations in the other patients. After 12

**Table 2** Changes in weight and waist circumference at month 6 and at month 12 for obese patients treated with placebo or diethylpropion (ITT, LOCF analysis)

Variable	6 months			12 months		
	Placebo	Diethylpropion	P-value	Placebo <sup>a</sup>	Diethylpropion	P-value
Weight; kg (95% CI)	-3.1 (-4.3 to -1.8)	-9.3 (-11.5 to -7.0)	<0.0001	-6.7 (-9.3 to -4.0)	-10.1 (-12.8 to -7.5)	0.07
Waist; cm (95% CI)	-2.3 (-4.0 to -0.6)	-8.8 (-11.1 to -6.5)	<0.0001	-4.6 (-7.2 to -2.1)	-9.2 (-11.8 to -6.5)	0.01

Abbreviations: CI, confidence interval; ITT, intention to treat; LOCF, last observation carried forward. <sup>a</sup>Placebo switched to diethylpropion on open-label phase (months 7–12).

months, no clinically significant abnormalities or worsening of baseline findings were observed. Echocardiogram was not performed in 5 out of 52 patients after double-blind phase and in 3 out of 36 patients after open-label phase.



**Figure 3** Number of patients achieving weight loss of 5 and 10% according to the group assignment at months 6 and 12. Placebo switched to diethylpropion on open-label phase (months 7–12).

### Psychiatric safety

Anxiety and depression were assessed using the Hamilton rating scales applied by experienced psychiatrists and no significant differences were observed between groups in the first 6 months (Table 5). During double-blind phase, one patient in placebo group presented depressive and anxiety symptoms at month 3 and was discontinued from the study. Another patient presented scores  $\geq 9$  in both Hamilton rating scales for depression and anxiety at month 6 and was not included on open-label phase. This patient was on diethylpropion group. During open-label phase (all patients on diethylpropion), one patient developed depression at month 9. This patient was first in the placebo group and switched to diethylpropion at month 6.

### Discussion

This study evaluated the efficacy and safety of diethylpropion for long-term use (1 year) and our results suggested that diethylpropion 50 mg sustained-release tablets BID were effective in reducing body weight and also favorably affecting several cardiometabolic risk factors. Our results have shown superior results as compared with those previously published.<sup>17–22</sup> In a recent meta-analysis, patients treated with diethylpropion lost an average of 3.0 kg

**Table 3** Changes in serum chemistries from baseline values for participants treated with placebo or diethylpropion (ITT, LOCF analysis)

Variable	Placebo*			Diethylpropion		
	Baseline	Month 6	Month 12	Baseline	Month 6	Month 12
Glucose (mmol l <sup>-1</sup> )	4.95 ± 0.44	4.91 ± 0.45	4.86 ± 0.41	5.04 ± 0.37	4.90 ± 0.42 <sup>‡</sup>	4.89 ± 0.48 <sup>‡</sup>
Insulin (pmol l <sup>-1</sup> )	100.7 ± 70.1	93.8 ± 68.1	84.7 ± 66.0	83.3 ± 35.4	67.4 ± 30.6 <sup>†</sup>	70.1 ± 40.3
HOMA-IR	3.0 ± 2.5	2.8 ± 2.4	2.64 ± 2.3	2.9 ± 1.0	2.3 ± 1.0 <sup>†</sup>	2.2 ± 1.1 <sup>†</sup>
Total cholesterol (mmol l <sup>-1</sup> )	4.76 ± 0.86	4.77 ± 0.97	4.65 ± 0.95	4.93 ± 0.98	4.63 ± 0.89 <sup>†</sup>	4.59 ± 0.90 <sup>†</sup>
HDL cholesterol (mmol l <sup>-1</sup> )	1.21 ± 0.28	1.30 ± 0.35 <sup>†</sup>	1.30 ± 0.34 <sup>†</sup>	1.26 ± 0.25	1.37 ± 0.30 <sup>†</sup>	1.39 ± 0.25 <sup>#</sup>
LDL cholesterol (mmol l <sup>-1</sup> )	2.93 ± 0.91	2.82 ± 0.93	2.70 ± 0.89 <sup>‡</sup>	2.92 ± 0.94	2.67 ± 0.74 <sup>‡</sup>	2.64 ± 0.80 <sup>‡</sup>
Triglycerides (mmol l <sup>-1</sup> )	1.44 ± 0.72	1.48 ± 0.89	1.41 ± 0.76	1.58 ± 1.01	1.21 ± 0.81 <sup>#</sup>	1.15 ± 0.75 <sup>#</sup>

Abbreviations: HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; ITT, intention to treat; LDL, low-density lipoprotein; LOCF, last observation carried forward. \*Placebo switched to diethylpropion on open-label phase (months 7–12). P-value vs baseline: <sup>‡</sup>P < 0.05; <sup>†</sup>P < 0.01; <sup>#</sup>P < 0.001.

**Table 4** Adverse events for obese patients treated with placebo or diethylpropion (double-blind phase)

Adverse event	0–3 months		P-value	3–6 months		P-value
	Placebo (%)	Diethylpropion (%)		Placebo (%)	Diethylpropion (%)	
Dry mouth	40.6	69.4	0.02	22.7	25.8	0.80
Insomnia	21.9	52.7	0.009	9.1	16.1	0.68
Constipation	25.0	38.9	0.22	9.1	22.6	0.27
Headache	25.0	33.3	0.45	4.5	9.7	0.63
Dizziness	9.4	13.9	0.71	4.5	9.7	0.63
Irritability	25.0	13.9	0.24	13.6	6.4	0.64
Tremor	6.2	8.3	0.90	0	6.4	0.50

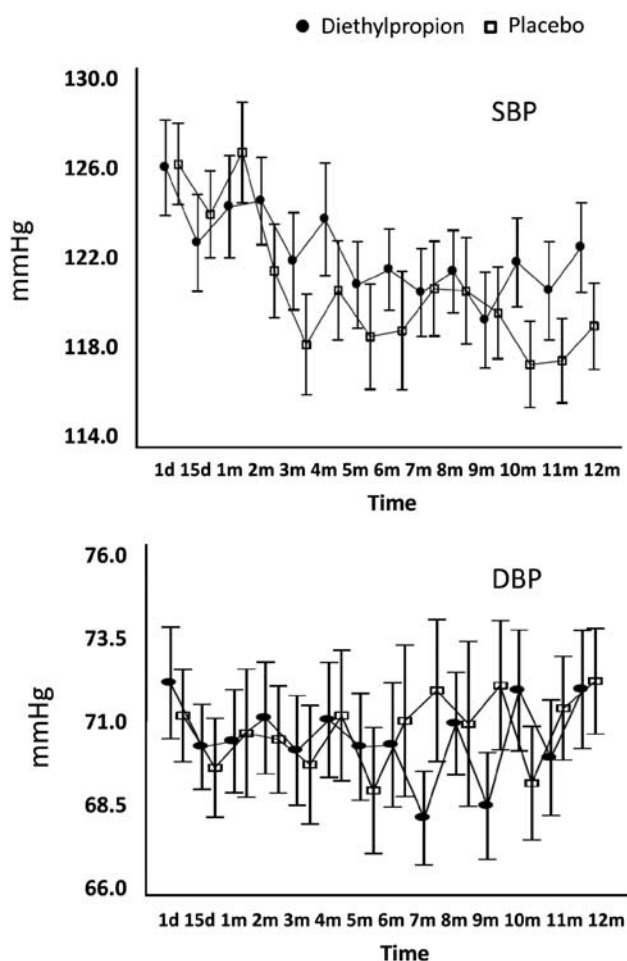
(confidence interval: -1.6 to 11.5 kg) of additional weight compared with placebo. The authors concluded that diethylpropion use in combination with lifestyle interventions was associated with a modest increase in weight loss of borderline statistical significance.<sup>23</sup> The reason for this difference must probably be the length of the study, as that in the meta-analysis, the duration of treatment with

diethylpropion varied from 6 to 52 weeks (mean: 17.6 weeks). Moreover, it is possible that our results have been superior because we have used a higher dosage than used in previous studies (100 vs 75 mg). According to the Latin America consensus on obesity, the daily recommended dose of diethylpropion is 40–120 mg per day.<sup>24</sup> The dosage of 50 mg BID was chosen because it is commercially available in our country.

In our study, diethylpropion produced a placebo-subtracted weight loss of -6.2 kg over 6 months. Our results were superior to the 2.9 kg net weight loss produced by orlistat and to the 4.2 kg net weight loss by sibutramine,<sup>25</sup> and were similar to that of a 6-month study with a new agent tesofensine—an inhibitor of the presynaptic uptake of noradrenaline, dopamine and serotonin.<sup>26</sup> Nevertheless, because of differences in design and population evaluated, we emphasize the need for some caution in comparing our results with other study results.

Diethylpropion is a sympathetic nervous system-stimulating drug. Studies have shown that obese subjects may present a defective sympathetic nervous system reactivity.<sup>27</sup> Recently, it was verified that reduced sympathoadrenal activity was a negative predictor of future body mass index after 18 years of follow-up.<sup>28</sup> Thus, the diethylpropion mechanism of action on sympathetic nervous system should be appropriate in obese patients.

Although diethylpropion is approved by the Food and Drug Administration for treatment of obesity since 1959, few studies had evaluated its use for more than 12 weeks. On the occasion of its approval, well-controlled investigations were not demanded. To determine the efficacy of various anorectic drugs in weight reduction, in 1970, the Food and Drug Administration required all manufacturers to obtain and submit in 6 months substantial evidence of their drug effectiveness from adequate and well-controlled clinical studies. For this reason, the studies, which had been conducted in response to the Food and Drug Administration request for 'substantial evidence' of the anorectics efficacy, ranged in duration from 3 weeks to 6 months, but few patients were exposed to a drug for more than 12 weeks.<sup>8</sup> Few studies with longer duration had been published.<sup>10–12</sup> The fact that these medications are no longer under patent and have a low cost may explain the limited interest from the pharmaceutical industry in carrying out long-duration clinical trials, at least to some extent.



**Figure 4** Systolic blood pressure (SBP) and diastolic blood pressure (DBP) during follow-up. Placebo switched to diethylpropion on open-label phase (months 7–12).

**Table 5** Hamilton rating scale for anxiety and depression changes for obese patients treated with placebo or diethylpropion

Variable	Baseline		3 months		6 months	
	Placebo	Diethylpropion	Placebo	Diethylpropion	Placebo	Diethylpropion
Anxiety	4.2 ± 2.0	3.9 ± 2.9	4.4 ± 3.5	4.3 ± 3.1	3.2 ± 2.6	4.0 ± 3.5
Depression	3.0 ± 2.3	3.3 ± 2.8	2.2 ± 2.3	3.2 ± 2.7	2.3 ± 2.1	3.1 ± 3.4

No significant differences were observed between groups.

On the other hand, obesity is a chronic disease and requires a continuous long-term treatment as seen in other chronic disorders, such as diabetes and hypertension, in which treatment is effective only for as long as the patients are receiving therapy.<sup>5</sup> At present, only sibutramine and orlistat are approved for long-term obesity treatment. Owing to the obesity epidemic, better evaluations of the available drugs have become essential. To our knowledge, this is the only long-duration sympathomimetic appetite-suppressant study that cautiously analyzed cardiovascular and psychiatric safety aspects.

On the cardiovascular aspect, the study population had a low cardiovascular risk. Owing to the sympathomimetic effect, an increase of blood pressure and pulse rate should be expected. However, no statistical differences were observed between the groups and no clinically significant ECG abnormalities in relation to baseline were observed in our patients. Diethylpropion appears to be safe for the treatment of obesity in patients with mild-to-moderate hypertension,<sup>29</sup> even in the presence of myocardial ischemia.<sup>30</sup> However, the drug should be used with caution or avoided in patients with severe hypertension or severe cardiovascular disease. Our data have shown low cardiovascular effects but it should be emphasized that the study population consisted of young healthy women and these results cannot be extrapolated to men, older patients, or patients with comorbidities.

Primary pulmonary hypertension has been associated with the intake of appetite-suppressant drugs, especially aminorex, dexfenfluramine and fenfluramine.<sup>31–33</sup> Serotonin contributes to the vasoconstriction and with pulmonary vessels remodeling, through a variety of mechanisms.<sup>34</sup> In relation to other appetite-suppressant agents (diethylpropion and phentermine), the data on their association with primary pulmonary hypertension are scarce, mostly arising from case reports.<sup>35,36</sup> As serotonin is the monoamine implicated in the genesis of vascular lesions and remodeling, the lack of association between primary pulmonary hypertension and diethylpropion may simply reflect the absence of serotonergic effect of this drug, which showed, together with phentermine, a much smaller effect in releasing platelet serotonin, as compared with aminorex and clorpheniramine.<sup>37</sup>

To our knowledge, this is the only study that used echocardiography as a marker of diethylpropion cardiovascular safety. There was no evidence of valvulopathy or pulmonary hypertension in the active drug groups. One patient in the placebo group showed a significant echocardiographic alteration (a 43 mm Hg of pulmonary artery pressure). She had a body mass index of 41.2 kg m<sup>-2</sup>. Post-mortem studies showed that obesity *per se* raises the risk of such findings.<sup>38</sup> There are evidences that sleep apnea, highly prevalent among the obese, predisposes to alveolar hypoxia with subsequent pulmonary vasoconstriction.<sup>39,40</sup> Thus, our findings support the hypothesis that diethylpropion is safe in terms of pulmonary hypertension.

On the psychiatric point of view, it is worth stressing out that the study population was very rigidly and carefully

selected by experienced specialists. This aspect somehow diminishes the 'surprise sensation' that could come with the positive psychiatric security data shown here (Table 5). Nevertheless, the fact that no severe psychiatric complication appeared in the study raises the possibility that diethylpropion potential of causing psychiatric syndromes is overestimated, at least for a well-selected population within the period of time described. Concordantly, no case of abuse/dependence was detected, as the drug was promptly interrupted at the end of the 12-month period by all patients. Appropriate criteria and appropriate algorithms to identify and quantify a psychiatrically safe population for such drugs are interesting points for further studies.

The medical literature has been reviewed in terms of reports of diethylpropion abuse.<sup>7</sup> Few reports are available and in most of the cases, the subjects carry a variety of psychiatric diagnoses such as inadequate, unstable, immature or hysterical personalities. As a rule, they had abused either amphetamines or phenmetrazine before diethylpropion had been tried. Thus, previous drug addiction and the presence of psychiatric disorders at any time should be well evaluated and should be considered as formal contraindications for the prescription of this drug in face of the available evidence.

Diethylpropion was generally well tolerated with adverse effects that were mostly mild and moderate. Dry mouth and insomnia were the most common adverse events observed, but no differences were detected between diethylpropion group and placebo after 3 months of treatment.

The limitations of our study are the small number of patients, the predominance of women and the fact that the study has been carried through in only one center, and these limit the generalization of the results. Therefore, these results cannot be extrapolated to men. Also, a low retention rate in all treatment groups, while consistent with previous studies in obese patients,<sup>41</sup> is a challenge in data analysis and interpretation. The use of the last observation carried forward approach to attribute missing values assumes that individual data at the time of dropout are representative of data at the end of the study if the participant had completed the study.<sup>42</sup>

In conclusion, 50 mg long-acting tablet BID of diethylpropion plus a standard dietary intervention produced sustained and clinically significant weight loss over 1 year. It seems to be safe under the cardiovascular and psychiatric point of view in a well-selected population. More studies are necessary with this medication as it is widely used in many countries and as obesity is a chronic disease that sometimes needs pharmacotherapy for a long period.

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## Conflict of interest

The authors declare no conflict of interest.

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