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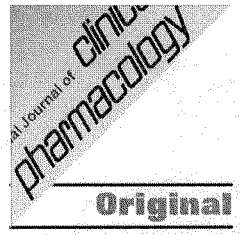

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Six-month efficacy and safety of amfepramone in obese Mexican patients: a double-blinded, randomized, controlled trial

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Key words
amfepramone – diethylpropion – Mexican, noradrenaline-releasing drug – obesity

Abstract. Amfepramone, also known as diethylpropion, is an anorectic drug used for the short-term treatment of obesity; however, its efficacy and safety during periods greater than 3 months has been scarcely studied. To evaluate the 6-month efficacy and safety of amfepramone treatment in obese adult Mexican patients resistant to diet and exercise, a double-blinded, randomized, and placebo-controlled clinical trial study was designed on 156 volunteers with a body mass index (BMI) greater than 30 kg/m^2 and less than 45 kg/m^2. Patients were randomized to receive a 75 mg tablet of amfepramone or placebo daily for 6 months. Primary outcome was the absolute body weight loss, whereas secondary outcomes were the percentage of patients who achieved at least 5% or 10% weight loss, as well as the improvement of anthropometric and metabolic parameters. Amfepramone treatment produced a superior efficacy to decrease body weight than placebo at 3 months (–4.9 ± 0.25 kg vs. –0.7 ± 0.32 kg) and 6 months (–7.7 ± 0.52 kg vs. –1.1 ± 0.7 kg). In addition, 64 and 34 patients achieved at least 5% or 10% weight loss, respectively, with amfepramone at 6 months, compared with 8 and 0 patients on placebo. Amfepramone also significantly improved BMI and waist circumference, but it only showed a favorable tendency in the waist-hip index (WHI), glucose, total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides, heart rate, systolic blood pressure, and diastolic blood pressure at 3 and 6 months. Amfepramone produced only mild adverse events, and they were presented in a greater number than placebo only at 3 months, dry mouth being the the main adverse event. Data suggest that amfepramone is effective and well tolerated in obese Mexican patients during a 6-month regimen.

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Introduction

Obesity is a major health problem worldwide. It is a chronic condition characterized by an excess of body fat more often attributed to long-term mismatches in energy balance, where daily energy intake exceeds daily energy expenditure [1]. Obesity is a risk factor for several chronic diseases, including hypertension, dyslipidemia, type 2 diabetes mellitus, sleep apnea, osteoarthritis, cardiovascular diseases, and some cancers [2, 3, 4]. In addition, a modest weight loss of 3% to 5% produces clinically meaningful health effects, and greater weight losses produces greater benefits [5].

The prevalence of obesity is alarming in Mexico and also in the United States of America (USA) where ~ 70% of adults are now either overweight or obese [6, 7]. The National Institute of Health in the USA has issued guidelines for obesity treatment, which indicate that all obese adults > 30 kg/m^2 of body mass index (BMI) and all adults with BMI ≥ 27 kg/m^2 and with obesity-associated comorbidities are candidates for drug treatment [8].

In the USA, only a few central action drugs, such as amfepramone or phentermine, are accessible for the short-term treatment of obesity (up to 12 weeks), whereas drugs such as orlistat, and recently lorcaserin and

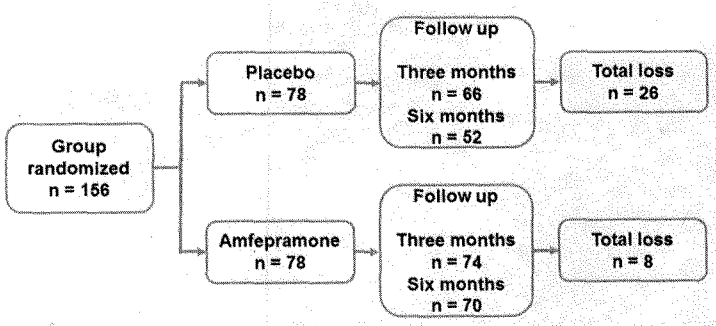

Figure 1. General outline of the study.

the mixture of topiramate and phentermine, are approved for longer treatments [9, 10]. Within central adrenergic drugs, it is considered that amfepramone, also known as diethylpropion, produces less central nervous system disturbance than most drugs in this therapeutic category. Moreover, it is also considered to be among the safest for patients with hypertension [10, 11]. It has been suggested that the anorectic effect produced by amfepramone is the result of its ability to enhance the release of adrenaline and dopamine from nerve terminals, as well as to inhibit their reuptake [11].

Amfepramone has been available for weight loss since the early 1960s [12]; however, the evidence of its efficacy and safety during periods longer than 3 months is limited in randomized controlled trials with large sample sizes [13, 14] and it has not been evaluated in obese adult Mexican patients resistant to lifestyle changes [15]. For the reasons described above, the current study was prompted to determine the 6-month efficacy and safety of 75 mg amfepramone daily treatment in obese Mexican patients resistant to diet and exercise.

Patients and methods

Subjects

To evaluate the 6-month efficacy and safety of oral administration of amfepramone in obese adult Mexican patients, 156 volunteers were recruited to perform a phase III, double-blinded, randomized, placebo-controlled clinical trial. The health status of patients was determined by medical history, clinical examination, and suitable laboratory tests. During the selection phase, 188 patients received medical support and were instructed to follow a hypocaloric diet to promote a deficit of 600 kcal per day. Moreover, subjects were also instructed to perform physical activity for 30 minutes per day. At the end of the selection phase, only 156 subjects were included in the trial phase, they were without comorbidities, over 18 years old, had a stable body weight and a BMI greater than 30 kg/m^2 and less than 45 kg/m^2, and were unresponsive to dietary and physical activity during the 3 months of the selection phase (body weight reduction less than 1 kg). In the trial phase, subjects received pharmacological treatment, and they were not controlled in regards to diet and exercise.

Exclusion criteria included hypersensitivity to sympathomimetic drugs, use of other antiobesity drugs, type 2 diabetes mellitus as well as any lung, kidney, liver, endocrine, or cardiac disease, psychiatric disorders, history of substance abuse or pregnancy.

This study was carried out following the recommendations of the latest version of the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [16]. All participants read the protocol, which was approved by the Institutional Research and Ethics Committees of the Escuela Superior de Medicina del Instituto Politécnico Nacional (Mexico, Distrito Federal) and Mexican Federal Commission for Protection against Health Risks (CAS/OR/01/CMN/113300410A0242-2651/2011), and provided written informed consent for their participation in the study.

Study design

After obtaining written informed consent, patients were randomly allocated to 1 of 2 groups to receive a tablet with 75 mg amfepramone (n = 78) or a matching placebo tablet (n = 78), for 180 days. All tablets were provided by Productos Medix, S.A. de C.V. (Mexico City, Mexico). Sample size calculation was estimated to provide 80% power to detect treatment differences in absolute body weight loss with an alpha level of 0.05, and

Table 1. Baseline demographic data.

Characteristic	Placebo (n = 78)	Amfepramone (n = 78)
Age (years)	39.1 ± 1.2	38.7 ± 1.1
Weight (kg)	88.3 ± 1.5	90.1 ± 1.5
Body mass index (kg/m^2)	34.9 ± 0.3	35.2 ± 0.4
Waist circumference (cm)	107.5 ± 1.1	109.0 ± 1.2
Waist-hip index (cm)	0.92 ± 0.01	0.93 ± 0.01

Data are expressed as mean ± SEM. There were no significant differences between studied groups by t-Student test.

a mean difference of 7 kg at 6 months with a standard deviation of 15.1 kg [13]. Figure 1 shows the general outline of the trial phase. All measurements were made at 0, 90, and 180 days of pharmacological treatment.

The primary outcome was the absolute mean body weight loss. Secondary end points included the number of patients who lost 5% or 10% of baseline body weight, waist circumference, waist-hip index (WHI), body mass index (BMI), heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as, glucose, total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides serum concentrations. In each determination, patients emptied their bladder upon arrival, dress was only a clinical robe, and a nude body weight was obtained on a calibrated scale. Height was determined with the patients placed with the heels together, and the buttocks, shoulders, and head in contact with the stadiometer. Waist circumference was measured at the level of the umbilicus due very heavy subjects (> 45 kg/m^2) were not included in the study, using a flexible metric tape without any pressure on the body, whereas the hip circumference was taken at the fullest part of the buttocks and over the end of the thigh bone. Measurements of systolic and diastolic blood pressure as well as heart rate were obtained using an electronic sphygmomanometer. Fasted glucose, total cholesterol, LDL, HDL, and triglycerides serum concentrations were determined by blood chemistry. In addition, at each visit, all patients were asked about adverse events, and a physical examination was performed.

Data analysis

Data were grouped by treatment and were analyzed based on the intent-to-treat population. Potential differences of demographic data between groups were assessed by Student t-test or χ^2-tests. Statistical analysis of the time courses obtained from the mean absolute body weight loss, waist circumference, WHI, BMI, heart rate, SBP, DBP as well as glucose, total cholesterol, LDL, HDL, and triglycerides serum concentrations were performed by two-way analysis of variance followed by Tukey's test, whereas statistical differences between groups regarding the number of patients with $\geq$ 5% or $\geq$ 10% body weight loss and the number of adverse effects or drop-outs were evaluated by χ^2 test. Differences were considered statistically significant when $p < 0.05$.

Results

Demographic data

Baseline demographic data on the patients are shown in Table 1. Amfepramone and placebo groups were equilibrated in terms of treatment, age, weight, height, BMI, waist circumference, WHI, heart rate, SBP, DBP, and blood chemistry variables. 156 subjects covered the inclusion criteria and were randomly distributed; the intent-to-treat (ITT) analysis was done in 78 subjects in each group. A greater proportion of subjects in the treatment group with amfepramone were maintained throughout the study. The 3-month and 6-month follow-up periods were completed by 84.6% (n = 66) and 66.7% (n = 52) of patients in the placebo group and 94.5% (n = 74) and 89.7% (n = 70) in amfepramone group, respectively. Regarding sex, women were the majority of participants, with 83.3% (n = 65) in the placebo group and 87.1% (n = 68) in the amfepramone group. There were no violations to the protocol that may have interfered with the study variables.

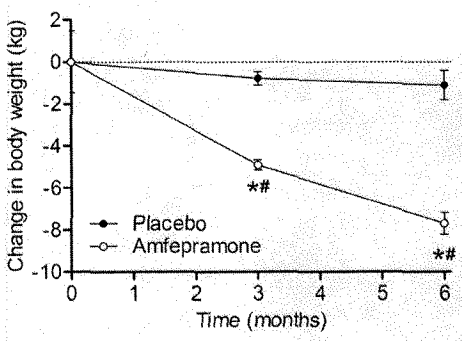

Figure 2. Time course of change in body weight obtained during 6 months in obese patients who received either placebo (black circles) or amfepramone (white circles). Data are expressed as mean ± standard error of the mean. *Significantly different from respective baseline value at time 0 and #significantly different between groups at the same time ($p < 0.05$), as determined by two-way analysis of variance with repeated measures, followed by Tukey's test.

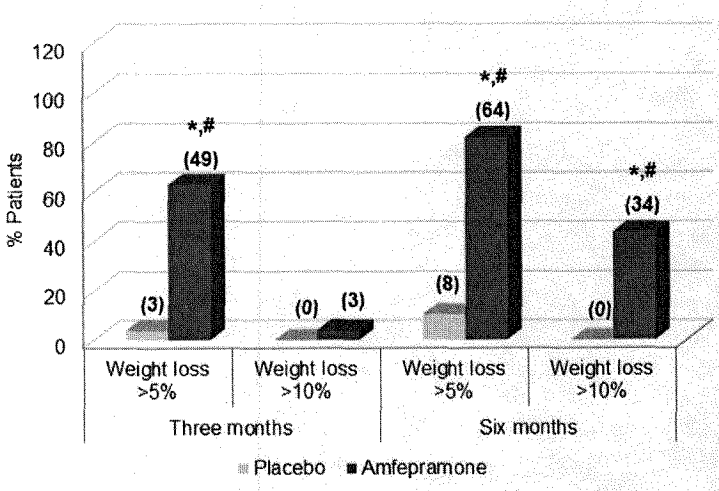

Figure 3. Percentage of obese patients who lost 5% or 10% of baseline body weight after receiving either placebo (white bars) or amfepramone (black bars) for 3 and 6 months. *Significantly different from respective baseline value at time 0 and #significantly different between groups at the same time ($p < 0.05$), as determined by χ^2 test.

Efficacy of 6-month amfepramone treatment on primary outcomes

Baseline mean body weights were 88.3 ± 1.5 kg for placebo and 90.1 ± 1.5 kg for amfepramone groups. Only amfepramone treatment produced a significant reduction of body weight values in a time-dependent manner ($p < 0.05$ by two-way analysis of variance, followed by the Tukey's test). After 3 and 6 months, participants treated with amfepramone lost a mean ± standard error of the mean of 4.9 ± 0.25 kg and 7.7 ± 0.52 kg using intent-to-treat analysis. In comparison, patients treated with placebo showed a reduction of initial body weight of 0.7 ± 0.32 kg at 3 months and 1.1 ± 0.7 kg at 6 months (Figure 2).

Efficacy of 6-month amfepramone treatment on secondary outcomes

Secondary outcome variables analysis showed that the percentage of patients achieving a 5% or greater body weight loss were 3.9% (n = 3) and 10.3% (n = 8) in the placebo group and 62.8% (n = 49) and 82.1% (n = 64) in the amfepramone group at 3 and 6 months, respectively. The percentages of patients in the amfepramone group were statistically different ($p < 0.05$ by χ^2-test) with respect to its own control and respect to placebo group in both times. In addition, amfepramone treatment reduced in a 10% or greater percentage the body weight of 3.9% (n = 3) and 43.6% (n = 34, $p \leq 0.05$) of patients at 3 and 6 months, respectively. On the contrary, no patient reached 10% of body weight reduction in the placebo group at any time (Figure 3).

Regarding BMI, the analysis showed that amfepramone treatment produced a significant time-dependent reduction ($p < 0.05$) in this parameter, while treatment with placebo only revealed a tendency to decrease BMI. With respect to waist circumference, amfepramone treatment, but not placebo, diminished in a significant manner the waist circumference over time. On the contrary, amfepramone treatment was not able to reduce WHI. In addition, amfepramone treatment was statistically superior to placebo in BMI and waist circumference at both evaluation times.

When the cardiovascular and metabolic variables were compared in relation to their baseline, it was found that HDL levels increased modestly in the amfepramone group, but not in the placebo group, at 3 and 6 months. Moreover, heart rate, SBP, DBP, total cholesterol, LDL, and triglycerides concentrations had only a tendency to decrease over time in the amfepramone group. Similar results were found with fasting glucose, where the corresponding levels decreased in a time-dependent manner, but without a statistical difference (Table 2).

Table 2. Values of secondary outcomes obtained from obese patients who received either placebo or amfepramone for 6 months.

Characteristic	Placebo			Amfepramone		
	Basal	3 months	6 months	Basal	3 months	6 months
BMI (kg/m^2)	34.9 ± 0.3	34.4 ± 0.3 **–0.5 ± 0.1**	34.4 ± 0.4 **–0.5 ± 0.1**	35.2 ± 0.4	33.4 ± 0.3* **–1.8 ± 0.2#**	32.1 ± 0.4* **–3.1 ± 0.2#**
Waist circumference (cm)	107.5 ± 1.1	103.8 ± 1.2 **–3.7 ± 0.6**	102.5 ± 1.4 **–5.0 ± 1.0**	109.0 ± 1.2	98.4 ± 1.3* **–10.2 ± 0.7#**	97.0 ± 1.3* **–12.3 ± 0.9#**
WHI	0.92 ± 0.01	0.91 ± 0.02 **–0.01 ± 0.01**	0.90 ± 0.03 **–0.02 ± 0.01**	0.93 ± 0.01	0.90 ± 0.02 **–0.03 ± 0.01**	0.90 ± 0.02 **–0.03 ± 0.01**
Glucose (mg/dL)	95.2 ± 2.0	93.3 ± 2.7 **–1.9 ± 3.3**	98.5 ± 3.1 3.2 ± 2.1	96.9 ± 0.8	93.9 ± 1.8 **–3.0 ± 1.9**	94.6 ± 1.0 **–2.3 ± 0.9**
Total cholesterol (mg/dL)	199.1 ± 6.4	203.6 ± 6.9 **4.5 ± 6.5**	206.1 ± 8.0 **7.0 ± 8.5**	196.3 ± 3.6	194.2 ± 4.9 **–2.1 ± 4.3**	191.0 ± 5.1 **–5.3 ± 2.9**
LDL (mg/dL)	121.3 ± 5.8	134.5 ± 5.9 **13.2 ± 6.0**	131.5 ± 9.9 **10.2 ± 7.4**	115.3 ± 3.4	116.9 ± 3.6 **1.6 ± 3.9**	108.0 ± 4.1 **–7.3 ± 2.4**
HDL (mg/dL)	44.1 ± 1.5	38.3 ± 1.2 **–5.8 ± 1.8**	37.0 ± 5.8 **–7.1 ± 7.3**	45.0 ± 0.9	47.1 ± 1.3 **2.1 ± 0.9**	48.3 ± 1.3 **3.3 ± 0.8**
Triglycerides (mg/dL)	168.4 ± 12.2	154.2 ± 12.5 **–14.2 ± 13.7**	188.1 ± 20.9 **19.7 ± 24.0**	180.0 ± 9.2	151.2 ± 8.6 **–28.8 ± 8.4**	173.5 ± 11.8 **–6.5 ± 8.3**
Heart rate (beats/min)	76.6 ± 5.8	75.3 ± 5.1 **–1.3 ± 3.8**	74.9 ± 5.3 **–1.7 ± 4.0**	76.0 ± 5.2	73.3 ± 5.1 **–2.7 ± 3.5**	71.8 ± 4.7 **–4.2 ± 3.2**
SBP (mmHg)	120.8 ± 6.1	119.9 ± 5.9 **–0.9 ± 5.4**	121.1 ± 6.3 **0.3 ± 5.5**	122.0 ± 5.6	119.6 ± 5.1 **–2.4 ± 3.7**	116.1 ± 4.7 **–5.9 ± 4.4**
DBP (mmHg)	78.3 ± 5.8	78.0 ± 5.4 **–0.3 ± 5.7**	78.2 ± 5.5 **–0.1 ± 5.4**	80.1 ± 5.1	77.9 ± 4.6 **–2.2 ± 4.1**	74.7 ± 4.3 **–5.4 ± 3.9**

Data are expressed as mean ± standard error of mean. *Significantly different from respective baseline and #significantly different from placebo at the same time ($p < 0.05$), as determined by two-way analysis of variance, followed by Tukey's test. Differences from respective baseline are given in bold numbers. BMI = Body mass index; WHI = waist-hip index; LDL = low-density lipoproteins; HDL = high-density lipoproteins; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 3. Drop outs from the placebo and 75-mg amfepramone groups.

Drop outs	Placebo (n =78)	Amfepramone (n = 78)
3 months	12	4*
6 months	14	4*
Total	26	8*
Lack of efficacy	17	1*
Loss to follow-up	9	5
Pregnancy	–	1
Food poisoning	–	1

*Significantly different from placebo group ($p < 0.05$) by χ^2 using intent-to-treat analysis.

Safety of 6-month amfepramone treatment

Both treatments were safe and well tolerated at 6 months, since only 2 patients in the amfepramone group were withdrawn from the study for severe adverse events, which were not related to drug treatment; 1 subject was withdrawn for pregnancy and other for food poisoning; the case of pregnancy was followed, and there were not complications for the mother or the newborn. In addition, 1 subject in the amfepramone group and 17 subjects in the placebo group were drop-outs from the study for lack of efficacy (body weight reduction less than 1 kg). Likewise, 9 subjects in the placebo group and 5 subjects in the amfepramone group were lost to follow-up. Table 3 shows the reasons for drop-outs from the study.

Other adverse events reported by patients were mild, including dry mouth, polydipsia, headache, constipation, and anxiety, dry mouth being the most common adverse effect at 3 and 6 months in either the placebo or amfepramone group (Table 4). Anxiety was manifested as passing concerns, sweating, and slight nervousness in the patients, and it did not affect their lifestyle, whereas dry mouth was characterized by the presence of thick saliva or a reduction in the salivary flow. Interestingly, the number of patients experiencing at least 1 adverse event was significantly superior in the amfepramone group (n = 54) with respect to the placebo group (n = 25) at 3 months, but not at 6 months (27 vs. 28, respectively).

Table 4. Mild adverse events reported by obese volunteers who orally received either placebo or amfepramone at 3 and 6 months.

Adverse event	Placebo		Amfepramone	
	3 months	6 months	3 months	6 months
Number of patients with at least 1 AE	25 (32.1%)	28 (35.9%)	54 (69.2%)*	27 (34.6%)
Polydipsia	1 (1.3%)	–	13 (16.7%)*	–
Dry mouth	23 (29.5%)	28 (35.9%)	35 (44.9%)	23 (29.5%)
Headache	1 (1.3%)	–	2 (2.6%)	2 (2.6%)
Constipation	–	–	2 (2.6%)	–
Anxiety	–	–	2 (2.6%)	2 (2.6%)

*Significantly different from placebo group ($p < 0.05$) by χ^2 using intent-to-treat analysis. AE = adverse event.

During the study, 38 patients took other medications, analgesics being the most used concomitant medications (33 subjects), followed by β-lactamic antibiotics (19 subjects), antiflu drugs (15 subjects), multivitamin (7 subjects), antigastroesophageal reflux drugs (3 subjects), antipruritic (1 subject), nitrofuran antibacterial (1 subject), antidiarrhea drug (1 subject), and laxative drug (1 subject). None of them showed any interaction with the pharmacological treatment.

Discussion

Treatment of obesity should not be for the short-term, but should be a long-term aim directed at attaining and maintaining normal body weight. Orlistat is the oldest drug approved by the Food and Drug Administration (USA) for longer treatments of obesity (> 12 weeks); however, it produces gastrointestinal adverse effects, such as diarrhea, bloating, and abdominal pain, which can be intolerable for some patients [8, 10, 17]. In addition, recent alerts of severe hepatic failure, pancreatitis, and renal oxalate calculi, should question its safety [9]. Other drugs, such as lorcaserin and the mixture of topiramate and phentermine, have recently been approved by Food and Drug Administration for the treatment of obesity, but their potential place on obesity therapy remains to be completely determined.

On the other hand, only a few adrenergic drugs are accessible in the USA for the short-term treatment of obesity [12]. Within this pharmacological group, amfepramone, an anorectic drug that exerts its effects in the brain, stimulating the release, as well as inhibiting the re-uptake of noradrenaline from the synaptic vesicles in the lateral hypothalamus, is considered one of the safest antiobesity drugs in terms of its toxic effects at a level of central nervous and cardiovascular systems [11, 13, 15].

In this study, the daily oral administration of 75-mg amfepramone for 6 months reduced, in a time-dependent manner, body weight, BMI, and waist circumference. In addition, 82.1% and 43.6% of patients achieved at least 5% and 10% of body weight loss, respectively. Notwithstanding, it only showed a tendency to improve WHI. Our data agree with a previous study performed in 60 patients over 7 months, which demonstrated that amfepramone is superior to placebo in reducing BMI and waist circumference [15]. Similarly, another study in 69 obese adults found that 50-mg amfepramone twice a day produced a sustained weight loss over 1 year [13]. In the same way, a randomized and placebo-controlled study performed in 174 obese premenopausal women showed that 75-mg amfepramone produced a greater weight loss and duplicated the number of patients achieving at least 5% weight loss than placebo by week 52 in the intent-to-treat population [14]. According to this, the report of the American College of Cardiology in conjunction with the American Heart Association Task Force on Practice Guidelines and the Obesity Society point out that a sustained weight loss of more than 3% produces clinically meaningful health benefits [5], therefore this study gives evidence in obese Mexican patients that amfepramone treatment not only reduced the body weight of these subjects, but also could improve their health in a clinically significant manner, when it is administered on a schedule of more than 12 weeks of treatment.

On the other hand, the placebo group did not reduce during the study body weight, BMI, waist circumference, nor WHI. Moreover, only 6.4% of patients reached at least 5% of body weight loss at 6 months. Contrary to our results, it has been reported in other 2 double-blinded, randomized, placebo-controlled trials evaluating the antiobesity effect of amfepramone, that the placebo group was able to significantly reduce body weight as well as other anthropometric parameters at 6 months [13, 15]. Such differ-

ences with our study could be explained on the basis of lifestyle changes because we only included patients previously unresponsive to recommended diet and exercise and because in the trial phase we did not control diet or exercise, as in the other studies, thus, the placebo administration in our study only produced a small change in body weight and other anthropometric parameters. In this regard, results suggest that amfepramone could be an antiobesity pharmacological option to treat refractory patients or patients with a poor adherence to diet and exercise.

It is well accepted that a modest weight reduction is beneficial in terms of reducing morbidity [5], controlling the components of metabolic syndrome, and decreasing the risk of developing type 2 diabetes mellitus and cardiovascular disease [5, 10, 18, 19]. After analysis of metabolic parameters, it was found that amfepramone only induced a positive tendency to improve glucose, total cholesterol, LDL, HDL, and triglycerides serum concentrations; however, it is fair to say that although these values were not statistically significant, they were in the borderline of significance. In line with these results, a previous study reported that 75-mg amfepramone for 7 months was able to decrease LDL and triglycerides, but without a statistical significance [15]. On the contrary, the oral administration of 100-mg amfepramone for 6 months improved glucose, total cholesterol, HDL, LDL, and triglycerides serum concentrations in a significant manner, and these parameters reached a better significance when they were analyzed at 12 months [13]. Differences between our study and the last study could be due to the doses used in each study (75-mg vs. 100-mg) or to the evaluated periods (6 months vs. 12 months). In addition, although amfepramone did not improve the metabolic parameters in a significantly statistical manner, it increased HDL and diminished LDL and triglycerides serum concentrations at values that could improve the health of patients. In this regard, it has been published that a weight loss greater than 5 kg produces clinically meaningful health benefits because it reduces triglycerides by 15 mg/dL, LDL by 5 mg/dL and increases HDL by 2 – 3 mg/dL [5], values clearly reached in our study with 75-mg amfepramone treatment. Contrary to lipid profile, amfepramone maintained fasting glucose levels without major changes; notwithstanding, the lack of a greater effect could be because all patients included in the study were non-diabetic. Furthermore, the absence of a significantly statistical improvement of metabolic parameters in our study may be attributed to data dispersion. Taken together, these data seems to suggest that 6-month amfepramone treatment decreases in a clinically important, but not statistically different, manner the metabolic risk factors associated to obesity. However, further studies are necessary to confirm this possibility.

Regarding amfepramone safety, in this study it was observed that the frequency of adverse effects was significantly greater in the amfepramone group compared to placebo at 3 months, but not at 6 months, which agrees with other studies that point out that most of the adverse events produced by amfepramone are presented at the beginning of the treatment [15], and that after 3 months, they are similar to the placebo group [13], indicating a development of tolerance to amfepramone-induced adverse events. In this regard, it is noteworthy to point out that amfepramone not only seems to reach a better efficacy during periods longer than 12 weeks, but also that its safety increases after 3 months. In our study, amfepramone generated only mild adverse events, dry mouth being the adverse event most reported, and no patients were withdrawn for drug-related serious adverse events. Similar results have been found in other studies, where dry mouth [15] and constipation [13, 14] were the most common adverse events.

In addition, it has been suggested that antiobesity noradrenaline-releasing agents can increase blood pressure and heart rate and are thus contraindicated in patients with cardiovascular disease. However, in this study, there were no reports of adverse events related to the cardiovascular system. In addition, heart rate and blood pressure in our study showed a favorable tendency to be reduced at values that could reduce a cardiovascular risk and, consequently, produce health benefits [5]. Accordingly, another two randomized double-blind placebo-controlled studies show that administration of amfepramone for periods longer than 3-months slightly decreased mean systolic and diastol-

ic blood pressure as well as heart rate during follow-up, and they were not different over time with respect to placebo [13, 15]. In fact, amfepramone seems to be safe in obese patients with mild-to-moderate hypertension or angina pectoris [20, 21], and its association with primary pulmonary hypertension is scarce [22, 23] and controversial [13, 24]. Notwithstanding, the drug should be avoided for precaution in patients with severe hypertension or severe cardiovascular disease.

In this study there were no cases of abuse or dependence as the drug was promptly interrupted at the end of the 6-month period by all patients. In a similar way, a longer-term amfepramone study reports the absence of cases of drug abuse or dependence [13]. In addition, the literature points outs that amfepramone is an infrequently abused antiobesity drug [25]. Notwithstanding, the presence of psychiatric disorders and previous drug addiction should contraindicate the prescription of amfepramone because in most of the cases of amfepramone abuse, the subjects were diagnosed with a variety of psychiatric disorders, such as immature or hysterical personalities, and they had abused of other amphetamines before amfepramone had been tried [13, 25].

Conclusion

Data suggest that amfepramone reduces body weight and tends to improve other anthropometric and metabolic parameters in obese Mexican patients in a safe manner; therefore, a 6-month amfepramone treatment can be considered an effective and safe option for the treatment of obesity in patients who do not respond to lifestyle recommendations (diet and exercise). However, the main limitation of this study is the lack of a comparative analysis on the 6-month efficacy and safety of amfepramone treatment with other centrally acting drugs for treating obesity, therefore larger double-blind and comparative clinical trials are necessary to establish a better benefit-risk profile of amfepramone in treatments longer than 3 months.

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Conflict of interest

The authors declare they have no conflict of interest.

References

[1] *Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG.* Central nervous system control of food intake. Nature. 2000; *404:* 661-671. PubMed

[2] *Nguyen DM, El-Serag HB.* The epidemiology of obesity. Gastroenterol Clin North Am. 2010; *39:* 1-7. CrossRef PubMed

[3] *Selassie M, Sinha AC.* The epidemiology and aetiology of obesity: a global challenge. Best Pract Res Clin Anaesthesiol. 2011; *25:* 1-9. CrossRef PubMed

[4] *Malnick SD, Knobler H.* The medical complications of obesity. QJM. 2006; *99:* 565-579. CrossRef PubMed

[5] *Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ, Jordan HS, et al; Obesity Society.* 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014; *129 (Suppl 2):* S102-S138. CrossRef PubMed

[6] *Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM.* Prevalence of overweight and obesity in the United States, 1999-2004. JAMA. 2006; *295:* 1549-1555. CrossRef PubMed

[7] *Gutiérrez JP, Rivera-Dommarco J, Shamah-Levy T, Villalpando-Hernández S, Franco A, Cuevas-Nasu L, Romero-Martínez M, Hernández-Ávila M.* Encuesta Nacional de Salud y Nutrición 2012. Resultados Nacionales. Cuernavaca - México: Instituto Nacional de Salud Pública (MX); 2012.

[8] *Delaet D, Schauer D.* Obesity in adults. Clin Evid (Online). 2011; 2011 pii: 0604. PubMed

[9] *Cabrerizo García L, Ramos-Leví A, Moreno Lopera C, Rubio Herrera MA.* Update on pharmacology of obesity: benefits and risks. Nutr Hosp. 2013; *28 (Suppl 5):* 121-127. 10.3305/nh.2013.28.sup5.6927 PubMed

[10] *Cheung BM.* Drug treatment for obesity in the post-sibutramine era. Drug Saf. 2011; *34:* 641-650. CrossRef PubMed

[11] *Arias HR, Santamaría A, Ali SF.* Pharmacological and neurotoxicological actions mediated by bu-

propion and diethylpropion. Int Rev Neurobiol. 2009; *88:* 223-255. CrossRef PubMed

[12] *Ioannides-Demos LL, Piccenna L, McNeil JJ.* Pharmacotherapies for obesity: past, current, and future therapies. J Obes. 2011; 2011:179674. PubMed

[13] *Cercato C, Roizenblatt VA, Leança CC, Segal A, Lopes Filho AP, Mancini MC, Halpern A.* A randomized double-blind placebo-controlled study of the long-term efficacy and safety of diethylpropion in the treatment of obese subjects. Int J Obes (Lond). 2009; *33:* 857-865. CrossRef PubMed

[14] *Suplicy H, Boguszewski CL, dos Santos CM, do Desterro de Figueiredo M, Cunha DR, Radominski R.* A comparative study of five centrally acting drugs on the pharmacological treatment of obesity. Int J Obes (Lond). 2014; *38:* 1097-1103. PubMed

[15] *Morín Zaragoza R, Lonngi Villanueva S, Ponce López ML, Alcaraz Ortiz R, Barragán Díaz Infante LA.* Eficacia y seguridad de amfepramona en liberación lenta como tratamiento de obesidad. Rev Mex Cardiol. 2007; *18:* 9-16.

[16] *World Medical Association Inc.* Declaration of Helsinki – Ethical principles for medical research involving human subjects. Available from: http://www.wma.net/en/30publications/10policies/b3/. Accessed: January 15, 2014.

[17] *Powell TM, Khera A.* Therapeutic approaches to obesity. Curr Treat Options Cardiovasc Med. 2010; *12:* 381-395. CrossRef PubMed

[18] *Aronne LJ.* Therapeutic options for modifying cardiometabolic risk factors. Am J Med. 2007; *120 (Suppl 1):* S26-S34. CrossRef PubMed

[19] *Bassand JP.* Managing cardiovascular risk in patients with metabolic syndrome. Clin Cornerstone. 2006; *8 (Suppl 1):* S7-S14. CrossRef PubMed

[20] *Seedat YK, Reddy J.* Diethylpropion hydrochloride (Tenuate Dospan) in combination with hypotensive agents in the treatment of obesity associated with hypertension. Curr Ther Res Clin Exp. 1974; *16:* 398-413. PubMed

[21] *Russek HI.* Control of obesity in patients with angina pectoris: a double-blind study with diethylpropion hydrochloride. Am J Med Sci. 1966; *251:* 461-464. CrossRef PubMed

[22] *Abramowicz MJ, Van Haecke P, Demedts M, Delcroix M.* Primary pulmonary hypertension after amfepramone (diethylpropion) with BMPR2 mutation. Eur Respir J. 2003; *22:* 560-562. CrossRef PubMed

[23] *Thomas SH, Butt AY, Corris PA, Egan JJ, Higenbottam TW, Madden BP, Waller PC.* Appetite suppressants and primary pulmonary hypertension in the United Kingdom. Br Heart J. 1995; *74:* 660-663. CrossRef PubMed

[24] *Di Sacco G.* Amfepramone does not cause primary pulmonary hypertension. Eur Respir J. 2004; *23:* 790-791., author reply 790-791. CrossRef PubMed

[25] *Cohen S.* Diethylpropion (tenuate): an infrequently abused anorectic. Psychosomatics. 1977; *18:* 28-33. CrossRef PubMed